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THE NORMAL PULMONARY ARTERIAL PRESSURE DURING THE FIRST YEAR OF LIFE

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THE published data on pulmonary arterial pressures in normal human beings between the ages of 2½ and 17 years[1] and between 18 and 66 years[2] show no important differences, the systolic level lying between 11 and 29 mm. Hg and the diastolic between 4 and 13 mm.

It has been suspected for many years that a gradual transition from the fetal state of high pulmonary artery pressure to this lower "adult" figure takes place in the human being during infancy. This supposition was based on gross anatomical observations of the pulmonary arteries in infant lungs[3] and on the changes in the ratio of lumen size to wall thickness of small pulmonary muscular arteries in normal infants during the first year of life.[4] Studies in newborn lambs, by contrast, have shown that pulmonary vascular resistance and consequently pulmonary arterial pressure fall within a few minutes of the lungs being ventilated after delivery.[5] Accompanying this change is the production of a left-to-right shunt from aorta to pulmonary artery through the ductus arteriosus, a phenomenon which exists in the lamb for at least twelve hours after birth and possibly longer. The evidence available until quite recently has seemed against this sequence of events in human beings. Continuous murmurs due to a left-to-right shunt through the ductus arteriosus have rarely been encountered clinically in the first few days of life in normal infants, nor has angiocardiography revealed patency of the ductus at this time.[6, 7] First suspicion of normal postnatal arteriovenous shunting through the ductus arteriosus came from dye dilution studies in newborn infants[8] while definite evidence of persistence of such ductal patency in human beings was obtained by differences in hand and foot blood oxygen saturations after birth.[9]

Additional information regarding the change of dynamics in the pulmonary circulation in human beings has been achieved only recently through direct measurements in very young infants shortly after birth.[10, 11]

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MATERIAL AND METHODS

As part of a study of the cardiovascular system in mongolism, a number of measurements were obtained in newborn and older infants with this disorder who were free of intracardiac defects, as shown by cardiac catheterization performed in each infant. Initially no sedative was administered. Subsequently premedication with a Phenergan-chlorpromazine-Demerol mixture previously described[12] was used. A No. 5 Lehman catheter was introduced into the main pulmonary artery from the saphenous vein at the groin and a No. 20 needle inserted into the femoral artery at that site. Pressures received by a capacitance electromanometer were amplified and recorded in a Sanborn Polyviso assembly. The average of the systolic and diastolic pressure was obtained electrically. The zero level was set at a point 5 cm. above the table on which the infant was lying.

RESULTS

The values for pulmonary and systemic arterial pressures of fifteen such infants under one year of age examined while breathing air are given in Table I. In all nine infants aged over 11 days the pulmonary artery pressure was within the so-called "adult" range. Further, in none of them was there evidence of any aortico-pulmonary shunt suggesting a patent ductus arteriosus.

Under the age of 12 days, however, the pulmonary arterial pressure was considerably higher. Variation both in the degree of this elevation and in its level in relation to age occurred within this group of six infants. Two had systolic values within a few millimeters of the adult range. One showed moderate elevation above that level and three had pulmonary arterial pressures whose systolic level closely approximated that obtained from the systemic artery. In no case did the mean pulmonary pressure exceed systemic. In four of the six infants indirect evidence of a patent ductus arteriosus was obtained from analysis of blood oxygen saturation values in the pulmonary artery. In these cases there was a rise in percentage saturation averaging 9 per cent from the blood obtained from the pulmonary artery over that obtained from the right ventricle. Direct evidence by catheterization of the ductus arteriosus itself was obtained in one instance, while in

TABLE I. THE PULMONARY AND ARTERIAL PRESSURES RECORDED AT REST, WHILE BREATHING AIR, IN FIFTEEN MONGOLOID INFANTS FREE OF INTRACARDIAC MALFORMATIONS

CASE	AGE	PULMONARY ARTERIAL PRESSURE		SYSTEMIC ARTERIAL PRESSURE	
		ACTUAL	MEAN	ACTUAL	MEAN
B. S.	2 da.	55/30	42	55/40	45
G. M.	5 da.	40/15	25	85/65	—
D. M.	6 da.	60/30	45	65/45	50
G. B.	10 da.	30/10	20	58/20	40
D. K.	11 da.	80/50	65	90/60	80
J. P.	11 da.	32/9	17	80/45	56
P. D.	21 da.	30/18	22	70/35	50
M. D.	31 da.	22/9	13	70/35	46
C. B.	3 mo.	17/6	11	65/40	55
A. L.	3 mo.	21/12	15	85/60	70
J. L.	5 mo.	19/9	15	95/55	70
V. M.	6 mo.	28/19	24	100/55	70
M. V.	7 mo.	24/15	19	72/43	50
M. R.	7 mo.	18/8	11	68/32	—
C. F.	9 mo.	18/8	11	90/45	58

another angiocardiography revealed its presence. Only one infant (B. S.) under the age of 12 days failed to have a demonstrable patency of the ductus arteriosus.

DISCUSSION

In human subjects between the ages of 2 weeks and 66 years the pulmonary arterial pressure is consistently and normally below 30 mm. Hg in systole. It is also established that the level of pulmonary arterial pressure may be above this range in the first eleven days of life. From our studies and others,[10] it is clear that there is a considerable variation in the rate of decline of pulmonary arterial pressure in the first two weeks of life. A greater number of measurements will be necessary before it may be stated at which day of life the majority of normal infants arrive at the mature level of pressure.

The presence of a functioning patent ductus arteriosus in five of six of our infants under 12 days and in all infants under 76 hours studied by Adams and Lind[10] is in agreement with the findings of Dawes and associates[5] in newborn lambs. In none of our cases was a continuous murmur audible at the time of study.

The factors likely governing the fall in level of the pulmonary artery pressure in the newborn infant are several but all are related to a decrease in pulmonary vascular resistance during this period. The earliest and most significant of these probably occurs with expansion of the lungs at the onset of respiration. Ventilation of the lungs of newborn lambs with a variety of gases (including nitrogen) usually achieves a decrease in pulmonary vascular resistance of between 50 and 90 per cent within five to ten minutes of the first respiration.[5] Measurement of respiratory dynamics of normal newborn infants has demonstrated a mature respiratory pattern of ventilation within one hour of birth.[13] This suggests that if it were possible to measure pulmonary vascular resistance in human beings at this particular time, a considerable decrease in resistance would be recorded. Following this initial change, a further, more gradual decline in pulmonary vascular resistance might be expected from the increasing ratio of the lumen size to wall thickness in small pulmonary muscular arteries which occurs in the first month of life.[14] Whether the presence of a significant aorticopulmonary shunt through the ductus contributes to a delay in the fall of pulmonary arterial pressure in some cases is debatable. It may be argued that with the particular anatomical condition of muscular arteries existing in the newborn lung there is a reduction in the capacity of the pulmonary vascular bed. Under such circumstances even a moderate increase in pulmonary blood flow such as may occur through the ductus at this time might be sufficient to elevate the pulmonary arterial pressure.

Since the ductus arteriosus easily admits a 2 mm. probe in only 3 per cent of fresh autopsies after the seventh day of life,[15] any role played by the ductus shunt is probably normally eliminated during the second week of life, a suggestion which the evidence from cardiac catheterization would appear to support.

SUMMARY

The pulmonary arterial pressure was recorded in fifteen mongoloid infants under one year of age, with

normal cardiovascular systems. A "mature" level of pressure in the pulmonary artery is achieved some time within the first two weeks of life, after which the levels and ranges of pressure in the lesser circulation are identical with those found in normal older children and adults. During the first two weeks of life the systolic pulmonary artery pressure is rarely at systemic arterial level but the values are considerably higher than those in the older subjects. Associated left-to-right shunts through a patent ductus arteriosus are also frequently demonstrable at this time.

The chief factors believed responsible for this decline of pulmonary arterial pressure in the first fourteen days after birth are in order of importance:

1. Ventilation of the lungs.
2. Changes in the ratio of lumen size to wall thickness of small pulmonary muscular arteries.
3. Closure of the ductus arteriosus.

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THE PATTERN OF RESPONSE OF PULMONARY AND SYSTEMIC ARTERIAL PRESSURES IN NEWBORN AND OLDER INFANTS TO SHORT PERIODS OF HYPOXIA

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THE pulmonary arterial pressure becomes elevated when normal animals[1-3] or human adults[4-7] breathe a gas containing low oxygen concentrations. For a variety of reasons it has not been possible to assume that the response would be of the same type or to the same degree in small infants and newborn infants. The small infant may still have an extensive medial hypertrophy of the small muscular pulmonary arteries.[8, 9] In addition, the ductus arteriosus continues to be patent in most newborn infants, contributing significantly to the pulmonary blood flow,[10-12] and in some instances the pulmonary artery pressure may not yet have fallen to the adult level.[12] The purpose of this study has been to determine the nature of the response to hypoxia in this young group.

MATERIAL AND METHODS

As part of a study of the cardiovascular system in mongolism, thirteen infants under the age of one year were studied. Group I consisted of eight infants aged 1 to 9 months (average age, 5 months). All showed normal cardiovascular systems in the preliminary catheter studies. Group II consisted of five infants aged 2 to 11 days (average age, 8 days). These showed no clinical evidence of heart disease but showed direct or indirect evidence of a persistent patent foramen ovale and ductus arteriosus.[12]

All the studies were done under local anesthesia, the infants sleeping or quietly sucking on a nipple throughout the procedure. As indicated in the table, several infants were studied twice, the second study being carried out under basal sedation with a Phenergan-chlorpromazine-Demerol mixture. If any restlessness occurred which might disturb arterial pressures, a period of up to ten minutes was allowed to elapse before continuing the study. Arterial and venous pressures were measured with an electromanometer and recorded by a Sanborn Polyviso assembly. The blood oxygen saturation was measured with a Cuvette oximeter[13] calibrated by Van Slyke gas analysis. After the preliminary cardiac catheterization[12] and a control period, the infant was given a mixture of 10 per cent oxygen in 90 per cent nitrogen to breathe for six minutes. During this period femoral arterial samples and

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TABLE I

CASE	AGE	PULMONARY ARTERIAL PRESSURE						SYSTEMIC ARTERIAL PRESSURE (FEMORAL)						OXYGEN SATURATION PER CENT					
		CONTROL—AIR		HYPOXIA 10% O_2 FOR 6 MIN.		100% OXYGEN		CONTROL—AIR		HYPOXIA 10% O_2 FOR 6 MIN.		100% OXYGEN		SYSTEMIC ARTERY			R.V.	P.A.	SHUNTS
		ACTUAL	MEAN	ACTUAL	MEAN	ACTUAL	MEAN	ACTUAL	MEAN	ACTUAL	MEAN	ACTUAL	MEAN	CONTROL AIR	HYPOXIA 10% O_2 FOR 6 MIN.	100% OXYGEN			
Group I																			
1. M. D.	1 mo.	22/9	13	28/14	17	22/9	16	70/35	46	62/42	--	70/45	--	96	69	99			
2. C. B.	3 mo.	17/6	11	21/7	14	14/9	11	65/40	55	60/40	50	80/50	60	93	79	93			
3. A. L.	3 mo.	21/12	15	35/20	27	18/9	14	85/60	70	80/50	55	100/60	75	94.5	65	98.5			
4. J. L.	5 mo.	19/9	15	40/24	30	--	14	95/55	70	100/60	75	110/70	85	93.	54.	97.5			
†	5 mo.	20/14	16	33/27	29	24/15	18	80/45	60	100/50	68	100/55	70	94.	55.	97.			
5. V. M.	6 mo.	32/18	25	50/30	36	33/21	25	105/60	78	110/60	78	110/70	90	96	51	99			
†	6 mo.	28/19	24	45/25	33	29/18	22	100/55	70	85/45	56	95/55	75	96	49	97			
6. M. R.	7 mo.	18/8	--	26/14	17	18/9	12	68/32	--	78/32	45	70/37	--	78	56	96			
7. M. V.	7 mo.	24/15	19	25/20	15	21/16	17	72/43	50	93/52	65	80/42	58	93	84	96			
8. C. F.	9 mo.	18/8	11	24/13	16	18/9	14	90/45	58	70/32	40	100/55	70	95	55	97			
Group II																			
1. B. S.	2 da.	55/30	42	70/40	50	50/20	35	55/40	45	45/33	40	65/48	55	93	33	96	Angiocardiographic evidence of a shunt		
2. D. M.	6 da.	60/30	45	65/35	46	65/35	46	65/45	50	58/35	45	60/45	47	92	46	100	77	88	42%
†	6 da.	70/35	50	75/42	52	--	--	66/45	52	65/40	50	70/43	50	--	39	100			
3. J. P.	11 da.	32/9	17	51/16	29	39/14	25	80/45	56	85/50	60	90/55	64	95	33	97	75	80	20%
†	11 da.	33/8	18	50/20	35	32/8	18	90/55	64	75/40	50	90/50	62	--	36	99.5			
4. D. K.	11 da.	80/50	65	75/40	50	95/55	70	90/60	80	55/30	35	85/50	70	83	32	100	69	79	41%
†	11 da.	70/45	55	62/42	50	29/17	22	70/45	55	45/30	35	50/35	45	--	31	99			
5. G. B.*	10 da.	30/10	20	35/5	20	30/10	20	58/20	40	58/15	35	58/20	40	97.5	70	97	66	78	27%
		30/5	20	35/10	25	--	--	--	--	60/25	40	--	--	--	75	--			

		RIGHT ATRIAL PRESSURE		
		MEAN	MEAN	MEAN
2. D. M.	6 da.	6	22	9

*Given 15 per cent oxygen for 10 minutes.

†Second study carried out with sedation of Largactil, Phenergan, and Demerol.

R.V., Right ventricle; *P.A.*, pulmonary artery; *shunt*, percentage of pulmonary flow coming from the aorta through the ductus arteriosus.

systemic and pulmonary arterial pressures were recorded at two-minute intervals. One hundred per cent oxygen was then substituted and after five minutes the sampling and pressures were repeated. Considerable care had to be taken in the administration of the low oxygen mixture to ensure that no "dilution" with room air occurred. The infant's head was placed deeply in a small plastic funnel and a flow of 8 to 10 liters per minute passed over his face. With a smaller flow, or with the head near the funnel outlet, the arterial oxygen saturation would only fall 10 to 20 per cent, and this small change invariably failed to affect the pulmonary or systemic hemodynamics.

RESULTS

Group I.—Hypoxia produced an average fall in the arterial oxygen saturation of 30 per cent below the control values (range of fall, 9 to 47 per cent). With the fall in arterial oxygen saturation there was an average rise in the mean pulmonary artery pressure amounting to 44 per cent of the basal pressure (range, 27 to 100 per cent increase), this change being much greater than any of the fluctuations observed in the control period (±5 mm. Hg variation). The systemic arterial pressure changes were insignificant, the average fall in the mean pressure (6 per cent) lying within the range of control variation (±15 mm. Hg). With 100 per cent oxygen there was a rapid rise in the arterial oxygen saturation to above 96 per cent and a fall in the pulmonary artery pressure to the control level.

Group II.—In the four infants receiving 10 per cent oxygen, hypoxia produced an average fall in arterial oxygen saturation of 55 per cent (range, 52 to 62 per cent) and an average rise in the mean pulmonary artery pressure of 17 per cent (range, –23 to +90 per cent). The mean systemic arterial pressure fell by 21 per cent (range, 5 to 45 per cent). The right atrial pressure rose by 300 per cent in one case at the height of anoxia. Breathing 100 per cent oxygen produced the same rapid rise in arterial oxygen saturation as was observed in group I; the systemic arterial pressure fell to a value usually lower than the controls. The fifth infant in this group was given 15 per cent oxygen to breathe. This lowered the arterial oxygen saturation to 70 per cent, raised the pulmonary artery pressure by 20 per cent in one study, and produced no effect during a second study. No significant effect on the systemic arterial pressure was seen.

The clinical response observed during hypoxia was of two types and appeared to be associated with the degree of arterial oxygen desaturation. As noted by other observers,[14-16] hypoxia with arterial oxygen saturations as low as 50 per cent appeared to produce mild somnolence in all infants. However, when the saturation fell to 40 or 30 per cent the infants gradually began to move and become restless, finally crying strenuously, sometimes in a gasping fashion. One infant had a period of apnea at the height of anoxia. The color did not appear to be a good indication of the degree of desaturation, pallor more than cyanosis being the rule.

DISCUSSION

The systemic and pulmonary arterial pressures in group I show the

same pattern of response to a short term in induced hypoxia as is seen in the adult.[4-7] In most cases there was little or no change in pressure until the arterial oxygen saturation fell below 70 per cent, the greatest pressure rises occurring when the saturation fell to 50 to 65 per cent (Fig. 1). Increases in the mean pulmonary arterial pressure of up to 100 per cent, induced by these saturations, are far greater than those produced in adult studies. It is of interest to note that this critical level of arterial saturation is the same as is found in the fetus at term. The two examples of small changes in arterial oxygen saturation and pulmonary arterial pressure encountered in the course of this study were early observations and in all probability were associated with the breathing of a higher concentration of oxygen than 10 per cent (see method).

The hemodynamic response in the infants of group II, all less than 12 days of age, differed from the adult pattern. Hypoxia with 10 per cent oxygen produced a precipitous fall in arterial oxygen saturation in all cases. In five studies this was accompanied by a fall in mean arterial blood pressure to a level below the mean pulmonary arterial pressure (Fig. 2). As the ductus arteriosus

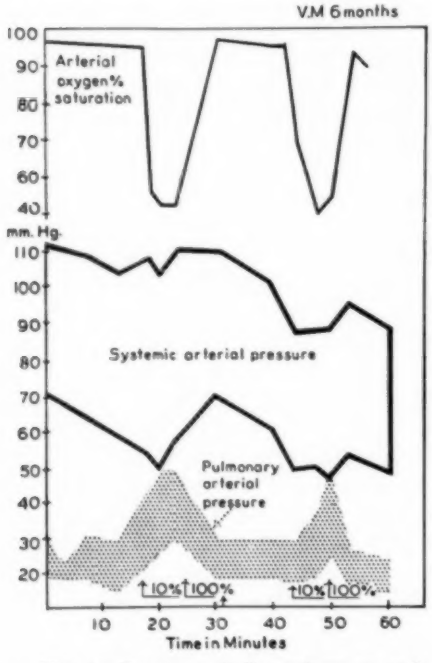

Fig. 1.—Response of the pulmonary and systemic arterial pressure to changes in arterial oxygen saturation of a 6-month-old infant. *Top line*, Arterial saturation; *open block*, systemic artery; *stippled block*, pulmonary artery.

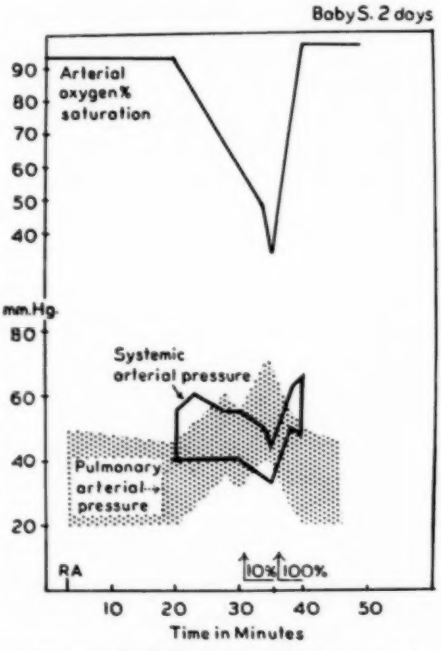

Fig. 2.—Response of the pulmonary and systemic arterial pressure to changes in arterial oxygen saturation in a 2-day-old infant. *Top line*, Arterial saturation; *open block*, systemic artery; *stippled block*, pulmonary artery.

had been proved patent in each of these infants, venous blood almost certainly was shunting from the pulmonary artery into the aorta during the hypoxic period. A comparable response in a patient aged 3½ years with patent ductus arteriosus and pulmonary hypertension has been noted by Burchell, Swan, and Wood[17] during the breathing of 10 per cent oxygen. Further evidence that this phenomenon occurs in normal infants is provided by the studies of Eldridge and Hultgren.[14] During a period of induced hypoxia there was a marked decrease in the foot capillary oxygen saturation compared to that in the hand. If such a venoarterial shunt was already present during crying in air, the anoxic stimulus increased it.

A precipitous fall in arterial oxygen saturation was also observed in J. P. As this infant had a relatively normal pulmonary arterial pressure which remained below the mean systemic arterial pressure throughout the study, a venoarterial shunt through the ductus arteriosus could not have occurred. However, a shunt through the patent foramen ovale might have caused the fall in saturation. In support of this the right atrial pressure was shown at the height of anoxia to be 300 per cent higher than the resting level in S. M., and to fall to resting levels within two minutes of giving 100 per cent oxygen. A similar rise in venous and fall in arterial pressure has been described in normal adults[18] and dogs[19] with induced low arterial oxygen saturation.

The presence of a large arteriovenous shunt through the patent ductus arteriosus, contributing as much as 50 per cent to the pulmonary flow in newborn lambs,[20] and the more recent evidence that such an arteriovenous flow occurs in newborn human infants[11, 12, 21] suggests a further cause for the precipitous fall in oxygen saturation observed in the present studies. Dawes has demonstrated that there is a fall in arterial oxygen saturation[20] when the ductus is tied in the lamb and when the pulmonary flow from this source is thus cut off. Any rise in pulmonary artery pressure with hypoxia will decrease the pressure gradient across the ductus from the aorta to the pulmonary artery and consequently reduce the pulmonary flow. Such a rise in pulmonary pressure has been shown to occur in the present studies.

Hypoventilation has been suggested as a cause for the fall in arterial oxygenation.[15] Experience in this clinic indicates that hypoventilation may be the result and not the cause of the low arterial oxygen level since the oxygen saturation falls within the first two or three minutes, before there is any significant reduction in respiratory rate or tidal volume.

The pulmonary arterial pressure responses to these low arterial oxygen saturations were varied. J. P., with a control pressure approaching the normal adult level, showed the same response as infants in group I, having a 70 and 90 per cent rise in pressure with hypoxia in two studies. Only small rises were seen in two infants where the control pressure was already high. The fourth infant, D. K., had a fall in pressure with hypoxia. However, the simultaneous fall in the systemic arterial pressure was much greater than the fall in the lesser circulation. This pressure relationship, together with the presence

of a large patent ductus, probably accounts for the response. If the pulmonary arterial pressure is expressed as a percentage of the simultaneous systemic pressure, the net result is actually a rise of 62 per cent. The fifth infant had little or no rise in pulmonary arterial pressure with mild hypoxia.

The variability of the pressure response to hypoxia in the lesser circulation of group II infants appears to be related to three factors: the degree of systemic arterial desaturation, the extent to which the pulmonary arterial pressure, high in fetal life, has fallen toward the adult level, and the size of the ductus arteriosus. These results indicate that if the neonatal circulatory adjustments involving the lungs and the ductus arteriosus have taken place, the response to hypoxia will be the same as in the older infants and adults. However, if this readjustment is incomplete, a short period of anoxia may produce a dramatic change in the circulatory dynamics, so that venous blood may by-pass the lungs at both the foramen ovale and ductus arteriosus level, producing a precipitious fall in arterial oxygen saturation. Angiocardiographic evidence indicates that this fetal pattern of circulation is present during the respiratory distress syndrome of newborn infants.[22, 23]

SUMMARY

The pattern of response of the systemic and pulmonary arterial pressures to short periods of induced hypoxia has been described in thirteen infants. In those infants with a normal pulmonary arterial pressure and a closed ductus arteriosus, a pressure rise in the lesser circulation occurred when the arterial oxygen saturation fell to fetal levels, there being little change until these saturations were reached. The response was considerably greater than has been reported for adults.

In those infants with evidence of an incomplete neonatal adjustment, hypoxia produced a precipitous fall in arterial oxygen saturation. Evidence for the re-establishment of the fetal pattern of circulation accounting for this severe desaturation has been presented.

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THE DUCTUS ARTERIOSUS IN THE NEONATAL PERIOD

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INTEREST has recently focused on the respiratory[1] and cardiovascular adjustments[2] of the neonate. While it has long been known that the patency and closure of the ductus arteriosus play a role in these adjustments and several anatomical surveys of the ductus arteriosus have been made,[3, 4] these analyses yield only nineteen[4] detailed neonatal ducti. Therefore from these surveys it has not been possible to obtain a picture of ductal closure in the newborn infant with any exactitude. Estimates of the time of closure have ranged from four days[6] to eight weeks.[3] It then seemed worth while to us to determine anatomically the degree of patency of the ductus arteriosus throughout the neonatal period. Much attention has been directed toward the supposed discrepancy between the anatomical and functional closure,[3] but without a foundation of anatomical measurement even this is in doubt.

MATERIAL AND METHODS

With seven unavoidable scattered interruptions one hundred consecutive neonatal hearts have been examined at post mortem. In order to render measurements more uniform these were fixed for twenty-four hours in formaldehyde and then measured in a uniform manner by one observer. A 2 mm. probe was inserted into the intact ductus and the degree of patency assessed as closed, snugly patent, easily patent, or widely patent. These terms were then correlated with measurements of the circumference of the opened ductus at pulmonary and aortic orifices and in the center of the ductus. The thickness of the walls and the internal circumference of the great vessels were measured 5 mm. distal to the valves. The internal circumference of the left subclavian artery was also measured, as was the thickness of the right and left ventricles. The age, clinical course, and anatomical cause of death were recorded.

The material collected has been broken into five groups according to the age at death. There were twenty-nine in the first group dying at 0 to 24 hours of life, thirty-nine dying between 1 and 4 days, twelve between 5 and 7 days, twelve between 8 and 15 days, and seven between 16 and 28 days.

FINDINGS

Table I gives the correlation of the terms of patency with the anatomical measurements.

One case of the one hundred studied was a truncus arteriosus and had no ductus arteriosus. The patency by age of the remaining ninety-nine is given

From the Research Institute of the Hospital for Sick Children.
Aided by a grant from the Ontario Heart Foundation.

in Table II. As was to be expected[7, 8] 40 per cent of our patients died between the first and fourth days. The number in the older age groups is correspondingly smaller, i.e., 12 per cent in the second week, 7 per cent in the third and fourth weeks. In order that all five groups may be considered on an equal basis, Table IV shows the patency by age expressed as a percentage of the total number of cases in each age group. It can be clearly seen in Table IV that the end of the first week is a critical time in the anatomical closure of the ductus. Before the seventh day 63 per cent of the cases were easily or widely patent; after the seventh day, 16 per cent were easily or widely patent. We will deal with the problems presented by the snugly patent ducti later. The three infants whose ducti were easily patent after the seventh day will be discussed in detail.

It was felt that respiratory or congenital heart disease sufficiently severe

Fig. 1.

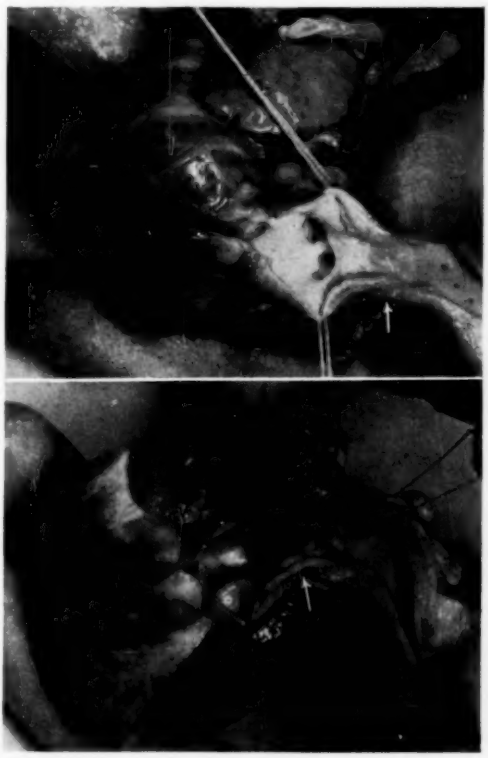

Fig. 2.

Fig. 1.—Widely patent ductus arteriosus. Death at 4 days of life from adrenogenital syndrome.

Fig. 2.—Closed ductus arteriosus. Death at 28 days of life from thrush and pneumonia.

to have caused death might have affected the normal closure pattern of the ductus arteriosus. Accordingly the fifty-five infants dying with respiratory or cardiac disease were excluded. The patency by age of the remaining forty-five is given in Table V. Table VI expresses this patency as a percentage of the total number of cases in each age group to the nearest whole figure. Again, before the seventh day 55 per cent of the ducti were easily or widely patent; after the seventh day, 7 per cent. This would suggest that pulmonary and cardiac abnormalities alone do not alter the normal time of closure of the ductus. Despite the problems of flow and function it can be seen that anatomically if a ductus arteriosus after the seventh day is more than snugly patent to a 2 mm. probe it is probably abnormally patent.

TABLE I. CORRELATION OF PATENCY WITH ANATOMICAL MEASUREMENTS

	AVERAGE CIRCUMFERENCE (MM.)	RANGE FROM SMALLEST TO WIDEST CIRCUMFERENCE (MM.)	
Snugly	6.5	3	8
Easily	8.8	4	11
Widely	10.6	5	13

TABLE II. CORRELATION OF AGE WITH PATENCY IN 99 CASES

	CLOSED	SNUGLY	EASILY	WIDELY
0-24 hr.	0	7	10	12
1-4 da.	3	8	15	13
5-7 da.	4	3	2	3
8-15 da.	4	6	2	0
16-28 da.	4	2	1	0

TABLE III. CORRELATION IN 99 CASES OF AGE WITH PATENCY WHERE OPEN INCLUDES SNUGLY, EASILY, AND WIDELY PATENT

	CLOSED	OPEN
0-7 da.	7	73
7-28 da.	8	11

Chi squared equals 10.79 and p equals less than 0.01.

TABLE IV. CORRELATION OF AGE WITH PATENCY EXPRESSED AS A PERCENTAGE OF THE TOTAL NUMBER OF CASES IN EACH AGE GROUP

	CLOSED	SNUGLY	EASILY	WIDELY
0-24 hr.	0	24	34	41
1-4 da.	8	20	39	33
5-7 da.	33	25	17	25
8-15 da.	33	50	17	0
16-28 da.	57	28	15	0

TABLE V. CORRELATION OF AGE WITH PATENCY IN INFANTS DYING OF NONPULMONARY AND NONCARDIAC DISEASE

	CLOSED	SNUGLY	EASILY	WIDELY
0-24 hr.	0	3	7	3
1-4 da.	1	4	5	3
5-7 da.	3	2	1	1
8-15 da.	3	4	1	0
16-28 da.	3	1	0	0

TABLE VI. CORRELATION OF AGE WITH PATENCY OF INFANTS DYING OF NONPULMONARY AND NONCARDIAC DISEASE EXPRESSED AS A PERCENTAGE OF THE TOTAL NUMBER OF CASES IN EACH AGE GROUP

	CLOSED	SNUGLY	EASILY	WIDELY
0-24 hr.	0	25	50	25
1-4 da.	7	30	38	25
5-7 da.	42	28	14	14
8-15 da.	37	50	13	0
16-28 da.	75	25	0	0

Of the one hundred patients examined, three had ducti easily patent after the seventh day. This degree of patency appears to be abnormal. Accordingly, clinical and pathological details of each of these cases are given below.

CASE REPORTS

CASE 1.—G. K. From birth this female infant showed abdominal distention. Laparotomy on the first day revealed inspissated meconium. Her postoperative course was poor and she died on the fourteenth day with an abscess in the right lobe of the liver and with peritonitis. At post mortem the lungs showed only a little pulmonary edema, some interstitial edema,

and a granular protein exudate peripherally. There was no increase in fibrous tissue and the arterioles appeared normal. The lumen to lumen plus media ratio was 0.68.[9] The heart apart from the widely patent ductus was normal. The pancreas showed typical changes of mucoviscidosis.

tory harsh, grade two, systolic murmur was heard maximal in the third left interspace; the pulmonic second sound was accentuated two plus and split. On fluoroscopy the heart was enlarged and the hilar flow appeared increased. The electrocardiogram showed right

Fig. 3.

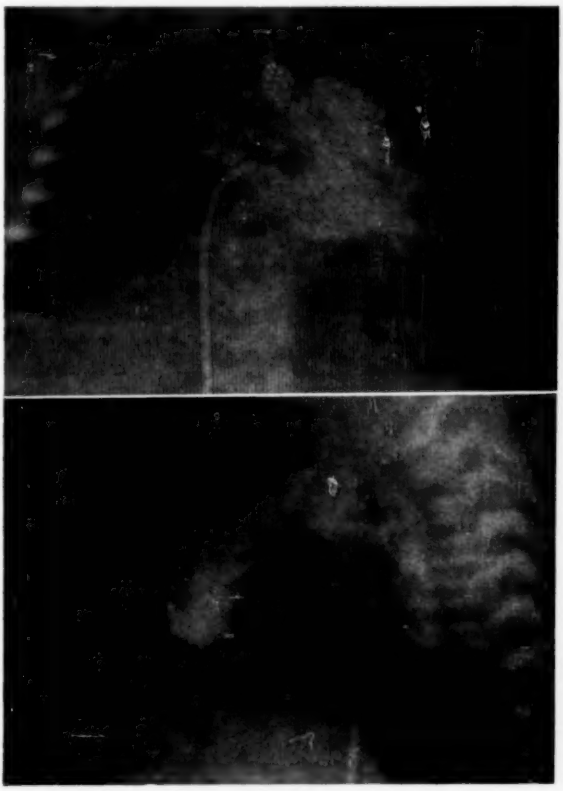

Fig. 4.

Fig. 3.—Posteroanterior view of the selective angiocardiogram from the right ventricle in Case 3, showing filling of the right ventricle, main pulmonary artery, ductus arteriosus, and descending aorta.

Fig. 4.—Lateral view simultaneous film with Fig. 3.

CASE 2.—A. O. This female infant was the first born of twins. She weighed 4 pounds 7 ounces, being of 36 weeks' gestation. Respiratory difficulties were present from birth; cyanosis was noted with crying. A transi-

auricular and left ventricular hypertrophy. The baby died in respiratory distress on the tenth day.

Post mortem showed heavy dark lungs oozing with blood; microscopically there was almost complete

collapse, and the arteries and arterioles were congested. The lumen to lumen plus media ratio was 0.66. The heart was twice the normal weight; the only anatomical defect was an aneurysmal dilatation of the ductus which was easily patent.

CASE 3.—G. P. This full-term mongolian infant was cyanosed from birth and showed a positive direct Coombs test. No cardiac murmurs were heard but the pulmonic second sound was markedly accentuated, and closely split. The electrocardiogram showed right auricular enlargement, right ventricular hypertrophy, and a marked right axis deviation.

Cardiac catheterization on the fourth day revealed a left-to-right shunt at the auricular, ventricular, and pulmonary artery levels. The aorta was entered through the ductus arteriosus. The main pulmonary artery pressure was 50/32, with a mean of 40. The aortic pressure was 60/40, with a mean of 45. The child died suddenly on the twenty-first day. That the ductus was functionally patent can be clearly seen in Figs. 3 and 4 from a selective angiogram done on the fourth day. This shows filling of a large main pulmonary artery, with filling of the descending aorta through the patent ductus.

Post mortem revealed an atrioventricular communis defect within the heart and an easily patent ductus. The lungs were somewhat firm but expanded. Microscopically they showed scattered areas of collapse with compensatory emphysema. The arteries and arterioles were markedly congested. The ratio of lumen to lumen plus media was 0.53.

DISCUSSION

From the data here assembled it can be seen that the end of the first week is a critical time in the anatomical closure of the ductus arteriosus. After that time only three infants, or 15 per cent of the cases in the 8- to 28-day group, remained easily patent and none were widely patent. It then appears that if the normal course of events transpires, the ductus arteriosus will be no more than snugly patent to a 2 mm. probe after the seventh day.

The problem of the functional patency in an anatomically snugly patent ductus cannot be solved here. Dawes and associates[5] have observed in the newborn lamb that a ductus whose lumen will barely admit the head of a pin can still carry nearly 40 ml. per minute of blood. This may well be true of the human ductus as well, for Rowe and James[2] have shown that in two of their patients at 10 and 11 days of age with no detectable cardiac abnormalities the pulmonary artery pressures were elevated and there was a moderate left-to-right shunt through the ductus. In both these infants approximately one-third of the total blood flow passed through the ductus. At 10 and 11 days of age one would anatomically expect the ductal lumen to be small.

The problem of the abnormally patent ductus as seen in the three infants with easily patent ducti at 10, 14, and 21 days of age is obviously a very complex one. The three case histories here outlined give some indication of these complexities. They are presented with the hope that as more and more such cases are reported in the literature some of the causative factors may become apparent.

SUMMARY

One hundred post-mortem neonatal hearts have been examined with regard to patency of the ductus. It has

been found that by the end of the first week the normally closing ductus will no more than snugly admit a 2 mm. probe. The problems of flow through such ducti and the mechanism of abnormal patency have been raised.

I am indebted to the Department of Pathology, the Hospital for Sick Children, Toronto, for the material on which this survey has been based; to Dr. L. Rosen for the measurement of the pulmonary arteriolar ratios in the three atypical cases; and to Dr. R. D. Rowe for his constant help and encouragement.

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Ruined Rum for Rheum.

November 11, 1759. I take Garlic Steeped in Rum against the Rheumatism. A coarse Medicine, but I submit to it, hoping for the Blessing of God upon it.

—EBENEZER PARKMAN DIARY.

CLINICAL AND PATHOLOGICAL OBSERVATIONS IN INFANTS WITH COARCTATION OF THE AORTA AND PATENT DUCTUS ARTERIOSUS

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THERE are few reports of blood pressure determinations in infants with coaretation of the aorta[1-7] because of the obvious difficulty in using the conventional auscultatory or palpatory techniques for blood pressure measurements in infancy. The "flush" technique described by one of us[2] has been found to be an easy, reliable procedure for routine blood pressure measurements in infants and has been used for the past four years on the wards at the St. Louis Children's Hospital. This technique has been especially helpful as a screening procedure in suspected cases of coaretation of the aorta. Since such infants are usually desperately ill upon admittance to the hospital, minimal diagnostic procedures can be done. Repeated attempts at auscultatory and palpatory blood pressure determinations are usually unsuccessful, but the application of the simple "flush" technique is easily accomplished. We thought it would be of interest to report the blood pressure findings and other observations in fourteen infants with coaretation of the aorta demonstrated at autopsy. The diagnosis was made ante mortem in all except two cases, and the "flush" technique was found to be a valuable procedure in establishing the diagnosis.

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MATERIAL AND METHODS

Fourteen patients with coaretation of the aorta from the St. Louis Children's Hospital, who had been autopsied in the Department of Pathology of Washington University, were selected for study. All of these had been observed during life by at least one of us. Blood pressure findings, electrocardiograms, roentgenograms of the chest, clinical notes, autopsy records, and microsections of the lung were available and were reviewed. Gross specimens of hearts and aortas preserved in formalin were also available from twelve of the fourteen patients. The patients ranged in age from 8 days to 8 months. All patients had coaretation of the aorta just proximal to the attachment of the ductus arteriosus and each had one or more defects permitting shunting of blood between the systemic and the pulmonary circulation.

Blood pressure determinations were made by the "flush" technique. This method has been described in detail previously[2] and briefly is accomplished by placing a pressure cuff around the wrist or ankle. The extremity is

blanched by a rubber dam and the cuff inflated. The pressure is then slowly released so that the fall is about 5 mm. Hg per second and the appearance of blood flow in the blanched extremity or "flush" represents the approximate systolic pressure.

RESULTS

The results of the blood pressure determinations are presented in Table I. In twelve of the fourteen patients there was a difference of 20 mm. Hg or more in the arterial pressure between the upper and lower extremities. Four patients had 10 mm. Hg or more difference between the right and left upper extremities, and two patients showed no gradient in pressure between the upper and lower extremities. Patient M. D. S. showed a gradient in pressure between the upper and lower extremities which was not sustained.

Electrocardiographic findings are presented in Table II. Nine of the thirteen patients on whom electrocardiograms were performed had evidence of right ventricular hypertrophy and myocardial disease. Two patients showed the changes associated with left ventricular hypertrophy.

Roentgenographic cardiac studies were performed upon eleven patients. All of these showed a marked degree of cardiac enlargement and nine patients also had pulmonary vascular engorgement.

The onset of symptoms was early in most patients. The commonest symptoms in order of frequency were poor feeding, dyspnea, tachypnea, and edema.

TABLE I. BLOOD PRESSURE BY THE "FLUSH" TECHNIQUE

PATIENT	AGE	RA	LA	RL	LL	FEMORALS
B. C. B.	6 da.	68	—	68	—	Weak
M. W. C.	1 wk.	—	70	—	70	Strong
R. D. R.	9 da.	64	68	32	36	Absent
S. L. G.	7 da.	140	120	105	100	Absent
J. M. F.	1 mo.	100	106	68	64	Weak
M. L. M.	5 wk.	130	120	45	40	Weak
N. E. R.	1 mo.	130	130	80	74	Absent
N. G. M.	5 da.	95	100	80	80	Weak
D. L. M.	2½ mo.	126	124	78	92	Not felt
V. L. R.	6 wk.	150	120	56	54	Weak
M. D. S.	3 mo.	112	118	68	76	Weak
		76	87	78	82	
D. A. C.	2 mo.	170	150	110	—	Absent
		87	86	50	52	
D. L. W.	7 wk.	122	124	94	80	Weak
K. P. A.	6 mo.	90	90	52	50	Weak

TABLE II. FINDINGS BY ELECTROCARDIOGRAPHY

PATIENT	FINDINGS
B. C. B.	No electrocardiogram
M. W. C.	Right ventricular hypertrophy
R. D. R.	Myocardial disease; right ventricular hypertrophy
S. L. G.	Myocardial disease; right ventricular hypertrophy
J. M. F.	Myocardial disease; right ventricular hypertrophy
M. L. M.	Myocardial disease; right ventricular hypertrophy
N. E. R.	Myocardial disease; right ventricular hypertrophy
N. G. M.	Within normal limits
D. L. M.	Myocardial disease; right ventricular hypertrophy
V. L. R.	Myocardial disease; left ventricular hypertrophy
M. D. S.	Within normal limits
D. A. C.	Myocardial disease; right ventricular hypertrophy
D. L. W.	Myocardial disease; left ventricular hypertrophy
K. P. A.	Suspicious of right ventricular hypertrophy

Some of the pathological findings are presented in Table III. The lumens of all their aortas were severely constricted in the coarcted segments. A horizontal ridge was demonstrable on the intimal surface of the coarcted segment at the attachment of the ductus arteriosus in all of twelve specimens. For comparison we examined hearts and aortas from six newborn infants with normal cardiovascular systems. Intimal ridges and severe constrictions were absent in these controls. The ducti arteriosi were patent in eleven of the fourteen cases of aortic coarctation. There were defects in the interventricular septa of nine and in the interatrial septa of five. One had a persistent truncus arteriosus. All of the patients had enlarged hearts as shown in Table III. Fibroelastic thickening of the ventricular endocardium was an associated finding in three patients (D. L. W., D. L. M., and K. P. A.). The microscopic appearances of the pulmonary arteries varied considerably from patient to patient; in two, the arteriolar muscle had completely disappeared (Fig. 1) and in five the muscular walls of the pulmonary arterioles were as thick as those normally found in newborn infants and in systemic arterioles (Fig. 2). Fibrous intimal thickening of small pulmonary arteries, characteristic of arteriosclerosis, was found in three patients. The arteriosclerotic lesions were minimal in two

TABLE III. ANATOMICAL DATA FROM THE PATIENTS WITH COARCTATION OF THE AORTA

PATIENT	AGE AT DEATH	THICKNESS OF PULMONARY ARTERIOLAR MEDIA*	FIBROUS INTIMAL THICKENING OF PULMONARY ARTERIES	CARDIOVASCULAR ANOMALIES†	THICKNESS OF RIGHT VENTRICLE WALL/LEFT VENTRICLE WALL (MM)	DIAMETERS OF AORTA‡ PROX.	ANT.	DIST.
B. C. B.	8 da.	Slight	None	I.V.; D.A.	3/3	15	10	20
M. W. C.	10 da.	Moderate	None	I.V.; I.A.; D.A.	4/4	-	2	-
R. D. R.	10 da.	Moderate	None	I.V.; D.A.	3/3	-	-	-
S. L. G.	24 da.	Slight	None	I.V.; I.A.; D.A.	9/8	5	2	3
J. M. F.	30 da.	Marked	None	I.V.; I.A.; D.A.	6/8	7	1	-
M. L. M.	35 da.	Marked	None	I.V.; I.A.; D.A.	5/7	5	2	5
N. E. R.	42 da.	None	None	D.A.	6/9	7	3	6
N. G. M.	42 da.	None	Advanced§	I.V.; D.A.	5/8	4	2	5
D. L. M.	2½ mo.	Moderate	None	I.A.	4/9	8	3	5
V. L. R.	2½ mo.	Moderate	None	D.A.	5/15	8	2	5
M. D. S.	3 mo.	Slight	Slight	I.V.; D.A.	4/8	7	3	5
D. A. C.	3 mo.	Marked	None	T.A.	6/9	4	2	5
D. L. W.	5½ mo.	Marked	None	D.A.	4/10	7	-	6
K. P. A.	8 mo.	Marked	Slight	I.V.	6/8	8	2	8

*"None" indicates that no muscle was present in arteriolar walls; "marked" indicates that the pulmonary arterioles had a smooth muscle wall as thick as that normally present in systemic arterioles.

†I.V. is interventricular septal defect; D.A. is ductus arteriosus; I.A. is interatrial septal defect; T.A. is truncus arteriosus defect. All patients had coarctation of the aorta just proximal to the ductus arteriosus, and all patients had marked cardiac hypertrophy.

‡Measurements are internal diameters that were taken at the narrowest point in the coarcted segment and 1 cm. proximal and 1 cm. distal to the coarcted segment. The dashes indicate that the specific measurement was not available and could not be obtained from the specimen.

§Numerous organized thrombi were also present in the small pulmonary arteries.

patients but advanced in one patient (N. G. M.), and in this patient numerous recognizable organized thrombi were found in the pulmonary arteries (Figs. 3 and 4).

congenital cardiac malformations. There are certain findings that, when present, should make one suspect that coarctation is one of the malformations present.

Fig. 1.

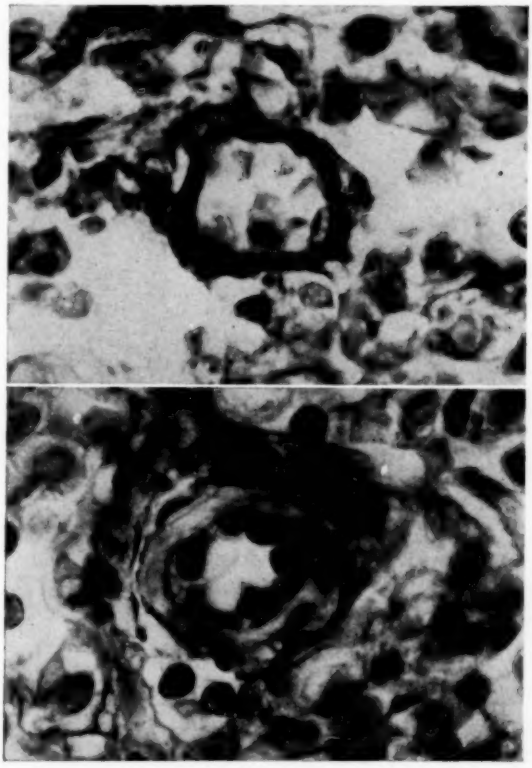

Fig. 2.

Fig. 1.—Patient N. E. R. A pulmonary arteriole or venule without smooth muscle in its wall. Arterioles with this structure are found normally after the early period of postnatal life, and can be distinguished from venules only by observing their origins from muscular pulmonary arteries in fortuitously cut sections. (Aldehyde fuchsin-van Gieson-iron hematoxylin; ×1200; reduced ⅛.)

Fig. 2.—Patient K. P. A. A pulmonary arteriole with a very thick muscular coat. This is definitely abnormal for an infant 8 months of age. (Aldehyde fuchsin-van Gieson-iron hematoxylin; ×1200; reduced ⅛.)

DISCUSSION

There is, of course, nothing unusual about the clinical picture of such patients that would definitely distinguish them from babies with other serious

The onset of symptoms was very early in life for most of our patients. A similarly early appearance was noted in the patients studied by Calodney and Carson.[5] Upon examination

one finds the patient in extreme distress. The color is ashen gray and respirations are rapid and labored. Edema may be present and may be

The electrocardiographic findings are by no means diagnostic. As can be seen in Table II, nine patients showed electrocardiographic evidence

Fig. 3.

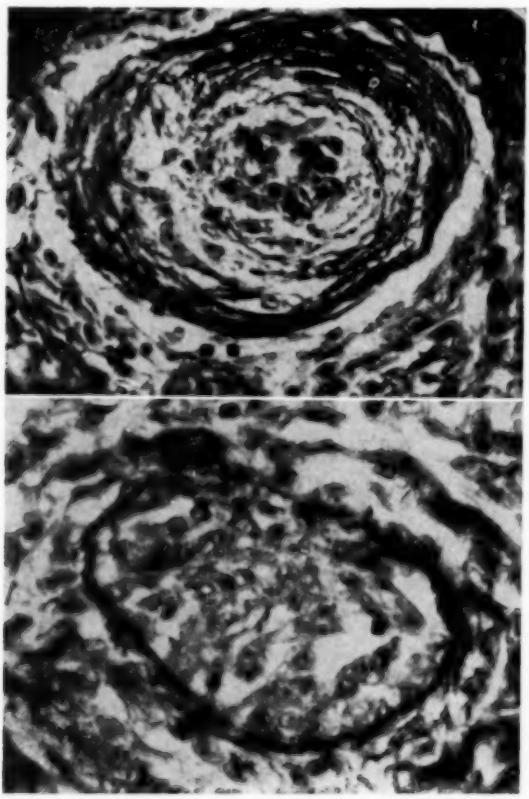

Fig. 4.

Fig. 3.—Patient N. G. M. A small pulmonary artery with the lumen markedly narrowed by fibrous intimal proliferation. The smooth muscle of the thin media can be seen with difficulty along a short segment of the arterial wall. (Aldehyde fuchsin-van Gieson-iron hematoxylin; ×450; reduced ⅛.)

Fig. 4.—Same patient as Fig. 3. The lumen of the small artery is almost completely occupied by proliferated endothelial cells. The smooth muscle normally present in the wall of such a vessel is not seen. This lesion probably represents an unusual reaction to pulmonary arterial thrombi. (Aldehyde fuchsin-van Gieson-iron hematoxylin; ×800; reduced ⅛.)

limited to the extremities, or it may be generalized. The heart is enlarged and the heart rate rapid. There is usually a loud, basilar systolic murmur. There may be scattered rhonchi and râles in both lungs. The liver and spleen are enlarged.

of right ventricular hypertrophy and myocardial disease. The criteria used for this interpretation were: (1) an intrinsicoid deflection in V_1 of .04 second or greater; (2) deep S wave in V_6. It was felt that these findings were sufficiently exaggerated so as not

to be confused with the expected right-sided electrocardiographic pattern usually seen in the first three months of life. The criterion used for the diagnosis of myocardial disease was T-wave depression or inversion. These electrocardiographic changes are demonstrated in Fig. 5. The demonstration of right ventricular hypertrophy by electrocardiography was substantiated by the finding at autopsy of greatly thickened right ventricular walls, as may be seen in Table III.

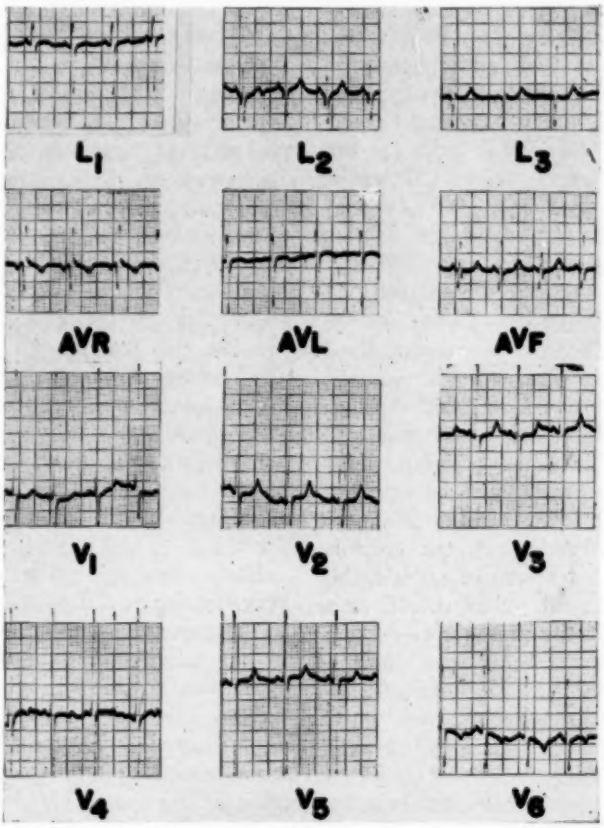

Fig. 5.—Patient D. L. M. Electrocardiogram showing right ventricular hypertrophy and myocardial disease.

Radiographic findings can be helpful in arousing suspicion that one may be dealing with a case of coaretation with other cardiac abnormalities, as pointed out in a previous publication.[8] The findings of pulmonary vascular engorgement and right ventricular hypertrophy in a baby with a difference of 20 mm. in pressure between the upper and lower extremities should make one very suspicious of coaretation of the aorta with an associated patent ductus arteriosus or other shunt between the systemic and pulmonary circulations. A number of other congenital cardiac malformations without associated coaretation may

produce a similar clinical picture. These conditions are endocardial fibroelastosis, anomalous origin of the left coronary artery associated with endocardial fibroelastosis, patent ductus arteriosus, large interatrial septal defect, and interventricular septal defect. By x-ray the first two conditions will not show pulmonary vascular engorgement indicative of a shunt, although in the presence of cardiac failure it may be difficult to distinguish pulmonary congestion from pulmonary vascular engorgement. In patients with the last three mentioned defects occurring either separately or together, it may be quite difficult to determine whether or not there is an associated coarctation of the aorta if the infants present themselves in congestive failure.

Palpation for the presence of femoral pulsations should be done as part of the physical examination. In four patients the femoral pulsations were absent, and in eight patients the pulsations were weak. In one patient, however, the femoral pulses were present and palpable. It can only be concluded that absent or questionably palpable femoral pulses should make one think of the presence of coarctation of the aorta, but a strong femoral pulse does not rule out the possibility. The presence of strong femoral pulsations may be explained by (1) only mild to moderate reduction in the aortic lumen at the site of the coarctation, (2) well-established collateral circulation, and (3) marked resistance in the pulmonary circulation with resultant right-sided hypertension that is sufficient to reverse the flow of blood through the patent ductus.

We have found that blood pressure determinations in the upper and lower extremities, as determined by the "flush" technique, are quite useful in establishing the diagnosis of coarctation of the aorta. In this series the correct diagnosis was made ante mortem in twelve of the fourteen patients. If we examine Table I, we see that in the majority of the patients a gradient of 20 mm. Hg or more was present between the upper and lower extremities. There were two exceptions. Patient M. D. S. demonstrated this gradient as an outpatient, but several days later, at time of hospital admittance, the gradient had disappeared. The disappearance of the gradient coincided with the onset of progressive, congestive heart failure. The explanation for this development may be that the failing left ventricle was incapable of keeping up the initially elevated pressure in the upper extremities. This explanation might also be used for patient B. C. B. who died shortly after admittance. In patient R. D. R., however, who was in congestive failure at the time of blood pressure determinations, the gradient persisted until death.

Eleven of the patients exhibited very definite evidence of hypertension in the upper extremities, but it should be pointed out that the absence of hypertension in the upper extremities does not rule out coarctation of the aorta, since six patients had normal blood pressure levels in their upper extremities.

In patients V. L. R., S. L. G., M. L. M., and D. A. C., there is a difference of 10 mm. Hg or more in pressure between the right and left upper extremities. This finding, when associated with hypotension in the lower extremities, should make one suspect the presence of the type of coarctation with a long coarcted segment of

the aorta that originates proximal to the origin of the left subclavian artery. In three of the above patients it was possible to demonstrate that the origin of the left subclavian artery was distal to the coarcted segment. In the one remaining patient, no adequate explanation was forthcoming to explain the difference in pressure determinations. Associated constriction of the lumen of the left subclavian artery at its origin, as described by Edwards,[9] was not seen in our cases.

Differential cyanosis has been cited as a helpful diagnostic aid in suspected cases of coarctation of the aorta and patent ductus arteriosus.[8, 9] Cyanosis of the lower portion of the body was not observed in this series or that of Calodney and Carson.[5] In one patient who showed no visible cyanosis, we demonstrated a slight but definite decrease in the arterial blood oxygen saturation in the lower extremities. Arterial oxygen saturation of the upper and lower extremities may be helpful, therefore, in establishing a diagnosis in a suspected case of coarctation with shunt. It is important to remember to take a blood sample from the right upper extremity, because occasionally the origin of the left subclavian artery may be distal to the coarcted segment and may receive venous blood from the pulmonary artery through a patent ductus arteriosus. It is also important to take the blood samples for analysis when the patient is inhaling room air. In a recent study on coarctation of the aorta associated with patent ductus arteriosus[22] it was shown that the direction of shunt can be changed by the amount of oxygen in the air. In three cases it was shown that the shunt of blood through the ductus was right to left when the patient was in room air, but, when the patient was inhaling oxygen, the shunt was left to right.

The reversal of flow through a patent ductus may also be demonstrated by intravenous angiocardiography, as was shown in a previous publication.[8] The use of this technique is not recommended routinely, however, and should be used only if a diagnosis cannot be established by other methods.

Even though a reversal of flow through the patent ductus arteriosus has been demonstrated by angiocardiography in previous studies, the explanation for this type of flow is not clear. Since there are few reported catheterization studies[19, 22] in infants with coarctation of the aorta, there is meager knowledge about the pressures in the right ventricle and pulmonary artery in such babies. In a previous publication[8] where reversal of flow was demonstrated, the pressure obtained by the "flush" technique in the lower extremities represents the approximate pressure in the pulmonary artery and is very definitely elevated. All babies except one (K. P. A.) were 3 months of age or less at the time of blood pressure determinations. It has been demonstrated that, in the initial neonatal period, there is normally slight right ventricular and pulmonary arterial hypertension.[20, 21] This gradually drops and during this period there is, in normal infants, a gradual disappearance of the muscular coat of the pulmonary arterioles[16] and a drop in pulmonary circuit resistance. It seems probable that the reversal of flow through a patent ductus must depend on the persistence of resistance in the pulmonary circuit of sufficient degree so that the pressure in the pulmonary artery will exceed that

of the aorta distal to the coarctation. Persistence of the fetal musculature in the pulmonary arterioles, sustained contraction of larger branches of the pulmonary arterial tree (muscular arteries, or advanced pulmonary arteriosclerosis could explain why a high resistance in the pulmonary circuit can be maintained. Examination of the microsection of lung, with special reference to pulmonary arterioles, was carried out with this in mind.

In one patient the maintenance of high resistance to flow in the pulmonary circuit could be accounted for on the basis of advanced pulmonary arteriosclerotic lesions and numerous organized pulmonary arterial thrombi (Figs. 3 and 4). In five patients the pulmonary arteriolar media was as thick as that found normally in systemic arterioles (Fig. 2), and the presence of such arterioles could account for the maintenance of high resistance in these patients. In the remaining eight patients the pulmonary arteriolar media was not as thick as that of systemic arterioles and a clear-cut anatomical explanation for high resistance in the pulmonary circulation was not found. However, sustained contraction of small muscular pulmonary arteries with or without some degree of muscular hypertrophy could account for increased resistance to flow. Such a physiologic mechanism has been suggested to explain the increased pulmonary circuit resistance in some patients with mitral stenosis who have no morphologic evidence of significant pulmonary arterial or arteriolar abnormalities.[17, 18]

When the diagnosis is established, treatment of infants with this type of complicated coarctation is very difficult. Medical management, which includes the usual regime of digitalization, oxygen, low salt formula, morphine as needed, antibiotic medication when indicated, and mercurial diuretics has not been successful in our hands.

In four of the babies in this series, an attempt at surgical correction was made, but they did not survive. Recently, however, we have had two infants, 6 and 4 weeks of age, who survived surgical correction of coarctation of the aorta and patent ductus arteriosus. The results are to be reported in a later publication. There are other reports of successful surgical correction.[11-14, 22]

There is divergence of opinion about the therapeutic approach in coarctation. Gross[15] reports that in none of the 400 patients with coarctation of the aorta he has operated upon was there a history of congestive failure in infancy. Nine patients with supposed isolated coarctation of the aorta from the same institution[4] were treated by medical management and survived an episode of congestive failure. He, therefore, recommends medical management rather than surgical intervention as the treatment of choice in infants with coarctation who develop congestive failure. Mustard,[11] on the other hand, reports that one-third of the cases of coarctation of the aorta seen by his group develop congestive failure early in infancy and respond so poorly to medical management that he recommends early surgical intervention. Neither author stresses the importance of the additional cardiac defects which are frequently present in coarctation of the aorta in infants who develop congestive failure. The presence of these defects probably accounts for the early development of

cardiac decompensation. As can be seen in Table III, all fourteen of our patients had associated cardiovascular defects; eleven had a patent ductus arteriosus, and nine had an interventricular septal defect. In the Calodney and Carson series, nineteen of the twenty-one patients had a patent ductus arteriosus associated with coarctation of the aorta. We feel that the presence of additional congenital defects (Table III) in our series played an important role in the unfavorable outcome and that surgical intervention is indicated as a lifesaving procedure. It is our feeling that, if a diagnosis of coarctation of the aorta is made in infancy and the patient is asymptomatic, surgical correction should certainly be delayed to a later age (8 to 10 years). We are presently following such a group of ten patients whose courses have been entirely uneventful.

The criticism of Gross[15] that an operation in infancy may have to be followed by a second surgical correction later in life is a valid one, but, if this initial surgical correction is carried out as a lifesaving procedure, then such criticism is not too important.

CONCLUSIONS

1. Fourteen patients under one year of age with proved coarctation of the aorta are reported and blood pressure findings, electrocardiograms, roentgenograms of the chest, clinical notes, autopsy records, and microsections of the lungs are reviewed.

2. The "flush" technique for blood pressure determinations is shown to be a practical, reliable aid in the diagnosis of coarctation of the aorta in young infants when a pressure gradient of 20 mm. Hg or more is present between the upper and lower extremities.

3. Associated cardiovascular defects were found at autopsy in all of the fourteen patients in this series. It is felt that this combination of defects might explain the development of congestive failure very early in life.

4. These babies respond very poorly to medical management, and surgical correction is indicated as a lifesaving measure.

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Down the Primrose Path

November 9, 1773. My Children have among them *The Life of Patty Saunders.* But whilst such amusements are apt to teach Amour & Intrigue, they are like to engage the Heart too far, and to consume too much time. . . The loose, gay Sentiments are also clothed in the ensnaring Language of this Age. . .

—Ebenezer Parkman Diary.

NITROGEN METABOLISM OF INFANTS FED HUMAN AND COW'S MILK

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HUMAN milk is the natural, and, as generally accepted, the ideal food for the human young. However, since breast feeding is not always possible or feasible, various modifications of cow's milk have been devised in the past thirty years in the hope of finding an entirely suitable substitute for human milk. Despite improvements in the techniques of preparation, indications remain that artificial cow's milk formulas are not well tolerated by some babies or are inadequate in some way; for example, infants fed on cow's milk may not resist certain infections as well as those on human milk.[1, 2] Proof of the superiority of breast feeding over cow's milk feeding, however, is not easily documented. One of the obvious differences between human and cow's milk is in the protein content[3] (3.2 to 3.8 Gm. per 100 ml. for cow's milk, and 1.1 to 1.5 Gm. per 100 ml. for human milk.)

One theory for the more satisfactory growth of the average infant on breast feeding suggests that the protein in human milk is biologically superior to the protein in cow's milk.[4] There may be other substances in human milk that have an effect on nitrogen retention; for example, a microbiological growth-factor (bifidus factor[5]) was recently found in human milk at a concentration of thirty to one hundred times the amount of the same substance in cow's milk. The possibility that this factor may play a part, directly or indirectly, in protein utilization has been discussed.[5, 6]

Since superiority in biological value of human milk protein would be indicated by greater retention of nitrogen from human than from cow's milk feeding, and one method of determining protein values is by use of comparative balance techniques, the present study was devised to demonstrate whether the protein of human milk is better retained or better metabolized than the protein of cow's milk, when the nitrogen content of both is similar. A secondary aim was an attempt to determine the minimal protein requirement of the growing infant. The effect of the biological value of cow's milk and of the bifidus factor newly discovered in both human and cow's milk was also studied in this series. The investigation resembled an earlier study conducted in premature infants,[7] but it differs from other previous studies[8] in which the milks were fed at higher protein levels.

METHOD

Nine healthy, full-term male infants less than 1 month of age were selected

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from an orphanage.* None had received human milk or antibiotics. The infants were studied, using a metabolic mattress, under relatively constant conditions of temperature, nursing care, and restriction of activity. Daily food intake was measured; total urinary output and fecal excretion were collected. For all infants the balance periods began after a feeding foreperiod of seven days, and were marked at three-day intervals by carmine. Collections were made continuously for each baby after he was placed on the bed.

The dietary regimen, in which feedings of specified dilutions of a standard commercial "humanized" cow's milk formula† and human milk were alternated, is outlined in Table I. Diets of all babies were supplemented with oral multiple vitamin drops.

Human milk was obtained from nursing mothers and frozen. When required for use, the milk was pooled and the nitrogen content measured. The milk was heated to 212° F. for fifteen minutes before feeding. The protein content of the cow's milk formula resembled that of human milk.

In an effort to approximate more closely the nitrogen content of both types of feeding, the human and cow's milks were diluted with water and the caloric content was equilibrated with equal parts, by weight, of an emulsion of vegetable oil (Lipomul) and lactose. For the diets very low in protein, both the human and cow's milk feedings were diluted (Table I).

Each type of feeding was given in such a way that adequate total collections for periods of nine to fifteen days were usually available for balance calculations. Except for Baby 8, the feeding order was: (1) cow's milk, nine to fifteen days; (2) human milk, nine to fifteen days; and (3) cow's milk, three to fifteen days.

Three additional babies (A, B, and C), selected in the same way as the initial group of nine, were fed the commercial cow's milk formula throughout the entire study (Table IV). In the first and last nine-day balances the infants were fed the unsupplemented cow's milk, and in the intermediate nine-day balance period, the human milk feeding was supplemented with the eluate of human milk adsorbed on charcoal columns,* 1.5 Gm. per liter. The milk eluate, similar to that used in an earlier study,[6] exerted a microbiological growth-promoting activity of 1 unit in 300 gamma for *Lactobacillus bifidus* var. *pennsylvanicus*.

One ill child, whose history is appended, was studied separately.

The feeding methods, sterilization of food, and collection techniques have previously been described in detail.[10]

Stool smears, pH, and culture† were examined periodically. Smears were counted for gram-positive and gram-negative organisms.[12]

Stools were dried with hydrochloric acid, acetone, and heat, and were pulverized and mixed before chemical analysis.

Nitrogen in the diet, urine, and stools was determined by the Kjeldahl

*The infants were studied at St. Vincent's Hospital for Women and Children, Philadelphia. Special acknowledgment is due His Excellency, Archbishop John O'Hara, of the Diocese of Philadelphia, the nursing staff, and Sister Eustolia, who was in charge of the infants observed.

†S. M. A., food formula for infants, was supplied by Wyeth Laboratories.

*Prepared[9] and furnished through the kindness of Dr. R. Kuhn of Heidelberg, Germany.

†Stools were cultured by Miss Nancy Minnick and Dr. Catharine S. Rose in our laboratory, as previously described.[11]

TABLE I. DIET AND BALANCE DATA FOR NINE INFANTS*

BABY NO.	DIET	DAYS ON DIET	BIRTH WT. (KG.)	WT.§ (KG.)	AGE (DA.)	AV. WT. GAIN‖ (GM./DA.)	N INTAKE GM./DA.	N URINE GM./DA.	N STOOLS GM./DA.	AV. DAILY BAL.	N RETENTION %
1	CM	9	4.06	4.20	23	5	1.72	0.37	0.22	1.13	66
	BM	9		4.25		15	1.41	0.25	0.16	1.00	71
	CM	9		4.39		22	2.11	0.54	0.27	1.30	62
				4.59							
2	CM	9	2.99	4.17	45	38	1.99	0.72	0.34	0.93	47
	BM	11		4.51		35	1.81	0.66	0.21	0.94	52
	CM	3		4.89		41	2.17	0.62	0.31	1.24	57
				5.03							
3	CM	15	3.46	3.15	12	16	1.42	0.36	0.22	0.84	59
	BM	15		3.39		53	1.73	0.43	0.30	1.00	58
	CM	15		4.17		37	1.88	0.66	0.31	0.91	49
				4.72							
4†	CM	9	3.60	3.47	12	18	1.27	0.40	0.17	0.70	55
	BM	9		3.63		20	1.26	0.32	0.18	0.76	61
	CM	9		3.81		15	1.29	0.50	0.17	0.62	48
				3.94							
5‡	CM	15	3.41	3.14	21	18	0.49	0.16	0.12	0.21	43
	BM	15		3.41		21	0.69	0.17	0.15	0.37	54
	CM	15		3.72		30	0.63	0.16	0.20	0.27	43
				4.17							
6†	CM	9	4.09	4.14	20	22	1.50	0.56	0.16	0.78	52
	BM	9		4.34		0	1.38	0.59	0.24	0.59	43
	CM	9		4.34		20	1.50	0.64	0.26	0.60	40
				4.52							
7‡	CM	15	2.65	3.04	19	0	0.44	0.15	0.14	0.15	34
	BM	15		3.01		25	0.54	0.20	0.13	0.21	39
	CM	9		3.38		52	0.51	0.16	0.09	0.26	51
				3.75							
8¶	BM	18	3.80	3.88	19	24	1.40	0.45	0.13	0.82	59
	CM	27		4.32		20	1.12	0.30	0.20	0.61	54
	BM	9		4.85		30	1.89	0.56	0.11	1.22	64
				5.13							
9	CM	15	3.12	3.70	21	11	1.06	0.57	0.16	0.33	32
	BM	15		3.86		5	1.04	0.67	0.12	0.25	24
	CM	15		3.94		0	0.98	0.56	0.12	0.30	31
				3.94							

							N URINE / N INTAKE	N STOOL / N INTAKE		
Av.	CM	13	3.46		22	16	1.22	33%	16%	51
	BM	13				22	1.32	33%	13%	54
	CM	11				28	1.34	36%	16%	48

BM, human milk; CM, cow's milk.

*Basic cow's milk formula was standard liquid S. M. A.: one can diluted with water to one quart.

†These babies were fed diluted formula: human milk was 2 parts water, 1 part milk; standard S. M. A. 1 part, water 3 parts.

‡These babies were fed diluted formula: human milk 1 part, water 1 part; standard S. M. A. 1 part, water 2 parts.

¶This baby was fed diluted formula: human milk, undiluted, standard S. M. A. 1 part, water 1 part. Feeding sequence was human milk—cow's milk—human milk.

§First three weights listed for each baby occurred at the start of the feeding of each new formula. Fourth weight listed was the final weight at the end of the last feeding period.

‖Average weight gain is actual weight gain during balance study.

method.[13] Creatinine was measured by the Jaffe reaction,[16] urea by urease,[14] and ammonia by aeration.[15] Total fat was determined by ether extraction.[10] Aliquots of all specimens were frozen before analysis. No allowance was made for losses caused by sweating.

RESULTS

Well Babies Fed Human and Cow's Milks.—Daily weight gain was small but relatively constant in all children during all types of feeding (Table I), averaging 16, 22, and 28 Gm. for the cow's milk, human milk, and cow's milk feedings, respectively.

The percentage of nitrogen retained by the infants fed human milk was slightly greater than that of infants fed cow's milk diluted to an equiprotein level (Table I). The periods of human milk feeding usually occurred between the two periods of cow's milk feeding. The nitrogen retention for the period on human milk averaged 54 per cent of the nitrogen fed. During the cow's milk feeding periods, retention averaged 51 per cent for the initial period and 48 per cent for the period following the human milk feedings. These differences in nitrogen retention were present in seven of the nine babies studied. The average nitrogen retention for all nine babies fed human milk exceeded by 30 mg. a day that of the babies fed cow's milk. (Table II).

TABLE II. NITROGEN RETAINED FROM HUMAN AND COW'S MILK

BABY NO.	N INTAKE*		N RETAINED*		(RETAINED)† (INTAKE)	EXPECTED ‡ RETENTION, CM	RETAINED-EXPECTED, CM
	BM	CM	BM	CM	BM		
1	4.24	5.75	3.02	3.64	0.71	4.08	−.44
2	5.39	6.10	2.77	3.02	0.51	3.11	−.09
3	5.18	4.96	3.01	2.74	0.58	2.89	−.15
4	3.78	3.85	2.31	1.98	0.61	2.35	−.37
5	2.05	1.69	1.08	0.76	0.53	0.90	−.14
6	4.15	4.54	1.67	2.11	0.40	1.82	+.29
7	1.61	1.39	0.64	0.53	0.40	0.56	−.03
8	4.70	3.35	2.86	1.84	0.61	2.04	−.20
9	3.13	3.06	0.73	0.95	0.23	0.71	+.24
							.100 ± .073

$t = 1.4$; $p = >.05$

BM, human milk; CM, cow's milk.

*Per three-day period.

†This table is designed to reduce mathematical errors for the statistical analysis. The column $\frac{\text{Retained}}{\text{Intake}}$ BM is similar in significance to the column "% retention" of Table I, during human milk feedings. Differences in numbers in the columns in the two tables represent mathematical differences. The data in Table II are averages of each three-day period. The data in Table I are these data divided by three to give daily average analyses.

‡This column indicates the amount of cow's milk nitrogen which would have been retained, if the baby retained cow's milk nitrogen at the same rate as human milk nitrogen. Calculations from these data reduce the standard error of the mean due to individual variations of the babies and to marked changes in intake.

Variations in nitrogen retention resulted mainly from differences in absorption rather than from differences in metabolism. Nitrogen excreted in the urine averaged 33, 33, and 36 per cent for cow's milk(period 1), human milk (period 2), and cow's milk (period 3) feedings, respectively, whereas stool excretion averaged 16, 13, and 16 per cent, respectively.

Urinary metabolites studied included urea, ammonia, and creatinine

(Table III). Urea and ammonia nitrogen averaged 70 per cent of the total urinary nitrogen during the first cow's milk feeding, 73 per cent during the human milk feeding, and 80 per cent during the second cow's milk feeding. The nitrogen:creatinine ratio averaged 1.1, 1.2, and 1.3 for all infants during the three feeding periods, respectively.

Urinary volume was greater during the period on human milk than during the cow's milk feedings, averaging 396, 443, and 376 ml. per day, respectively, during the first period on cow's milk, the period on human milk, and the second cow's milk feeding. Fluid intake during these periods averaged 524, 576, and 513 ml. respectively. Therefore, water retention and water losses, other than in the urine, during these periods were approximately equal.

TABLE III. URINARY NITROGEN PARTITION—DAILY AVERAGE

BABY NO.	DIET	VOL.	TOTAL N (GM.)	UREA (GM. N)	AMMONIA (GM. N)	CREATININE (MILLIMOLES)	N × 10 / CREATININE	AMMONIA + UREA / TOTAL N
1	CM	222	0.37	0.20	0.07	3.5	1.1	0.73
	BM	314	0.25	0.14	0.04	2.7	0.9	0.72
	CM	312	0.54	0.28	0.20	4.4	1.2	0.89
2	CM	394	0.72	0.49	0.06	4.2	1.7	0.76
	BM	524	0.66	0.50	0.08	4.8	1.4	0.88
	CM	298	0.62	0.48	0.08	3.2	1.9	0.90
3	CM	689	0.36	0.16	0.09	3.1	1.2	0.70
	BM	696	0.43	0.29	0.08	2.9	1.5	0.86
	CM	694	0.66	0.49	0.08	4.7	1.4	0.86
4	CM	242	0.40	0.26	0.05	3.5	1.1	0.78
	BM	239	0.32	0.18	0.05	3.7	0.8	0.72
	CM	261	0.50	0.25	0.07	3.9	1.3	0.64
5	CM	352	0.16	0.08	0.04	2.6	0.6	0.75
	BM	390	0.17	0.09	0.04	2.8	0.6	0.76
	CM	358	0.16	0.08	0.04	2.7	0.6	0.75
6	CM	262	0.56	0.33	0.05	3.8	1.5	0.68
	BM	270	0.59	0.35	0.06	4.3	1.4	0.70
	CM	292	0.64	0.33	0.10	4.8	1.3	0.67
10	CM	450	0.15	0.07	0.03	2.9	0.5	0.67
	BM	538	0.20	0.12	0.04	3.1	0.6	0.80
	CM	387	0.16	0.07	0.03	3.2	0.5	0.62
11	BM	615	0.45	0.21	0.05	3.4	1.3	0.58
	CM	603	0.30	0.13	0.06	4.2	0.7	0.63
	BM	527	0.56	0.32	0.06	4.3	1.3	0.68
12	CM	347	0.57	0.30	0.02	4.4	1.3	0.56
	BM	312	0.67	0.29	0.02	4.2	1.6	0.46
	CM	392	0.56	0.39	0.02	3.1	1.8	0.73
Av.	CM	396	0.40	0.22	0.05	3.6	1.1	0.70
	BM	443	0.43	0.26	0.05	3.6	1.2	0.73
	CM	376	0.48	0.30	0.08	3.8	1.3	0.80

BM, human milk; CM, cow's milk.

The stools were acid on both diets, with a pH averaging 5.5 in the period on human milk, and 5.7 during cow's milk feedings. Fat retention was 89 to 95 per cent in all the babies during both types of feeding.[10]

The stools of four infants were cultured for the presence of the human milk-sensitive organism, *L. bifidus* var. *pennslyvanicus*.[11] Babies 5, 7, and 9 had none of these bacteria in their stools during the initial fifteen-day feeding period on cow's milk. Babies 5, 7, 8, and 9 excreted large numbers of the organisms during the human milk feedings at five, ten, and fifteen days following the cow's milk feedings. Babies 7 and 9 had a few and baby 8, many, of *L. bifidus* var. *pennsylvanicus* in the stools for as long as two weeks after substitution of the dilute cow's milk mixture for human milk.

Supplementation of Cow's Milk With Human Milk Eluate.—No consistent increase in nitrogen retention over the retention seen in the period on the cow's milk formula alone occurred during the period in which cow's milk supplemented with human milk eluate was fed three babies (Table IV). Retention in the initial period on unsupplemented cow's milk averaged 48 per cent and in the final period without supplementation, 36 per cent. Nitrogen retention in the period of supplemented feedings averaged 46 per cent.

During human milk eluate supplementation a consistent change in the pH of the stools occurred which averaged 6.1 and 6.0 in the periods of unsupplemented feedings, and 5.7 when the dilute cow's milk was supplemented with the eluate.

TABLE IV. BALANCE DATA: DILUTE COW'S MILK SUPPLEMENTED WITH MILK ELUATE

BABY NO.*	DIET*	BIRTH WT.	WT.† KG.	AV. WT. GAIN‡ (GM./ DA.)	N INTAKE (GM./ DA.)	N URINE (GM./ DA.)	N STOOL (GM./ DA.)	AV. DAILY BAL.	% RETENTION	pH STOOL	URINE N MG. CREATININE
A	CM	2.95	3.01	19	1.13	0.46	0.17	0.50	44	6.2	1.4
	ME		3.18	21	1.19	0.46	0.22	0.51	43	5.6	1.2
	CM		3.37	17	1.18	0.57	0.24	0.37	31	6.1	1.4
			3.52								
B	CM	2.76	2.84	12	1.12	0.36	0.24	0.52	45	5.8	1.0
	ME		2.95	22	1.13	0.41	0.25	0.47	42	5.6	1.0
	CM		3.15	12	1.08	0.44	0.26	0.38	35	6.0	1.2
			3.26								
C	CM	3.34	3.32	50	1.25	0.41	0.19	0.65	52	6.3	1.1
	ME		3.77	7	1.23	0.38	0.20	0.65	53	5.9	1.0
	CM		3.83	5	1.22	0.44	0.29	0.49	40	6.0	0.9
			3.88								
Av.	CM			27	1.17	0.41	0.20	0.56	48	6.1	1.2
	ME			17	1.18	0.42	0.22	0.54	46	5.7	1.1
	CM			11	1.16	0.48	0.26	0.42	36	6.0	1.2

*Cow's milk (CM) = S. M. A.; milk eluate (ME) = S. M. A. supplemented with 1.5 Gm. milk eluate per liter. Each feeding period was 9 days. Baby A was 17 days old at start; B, 8 days; C, 19 days.

†First three weights listed for each baby are the weights at the start of each new formula feeding. Fourth weight listed is the final weight at the last feeding period.

‡Average weight gain is actual daily weight gain during balance study.

Balance Data on Ill Child.—During the course of this investigation Baby R. S. was admitted to the Hospital of the University of Pennsylvania with apparent food intolerance and was placed on a similar balance study (Table V). The data were not included in the earlier series.

R. S., a 6-week-old male infant, was admitted because of generalized edema of five days' duration. He had been delivered after a normal pregnancy,

and weighed 6 pounds 8 ounces at birth. He was placed on an evaporated milk-Karo formula and was discharged at one week weighing 6 pounds 3 ounces. A severe rash developed one week later, and the formula was changed to Mull-Soy and water. The rash gradually disappeared, but the patient began to vomit variable quantities of the feedings. On admission to the hospital he was taking 16 ounces Mull-Soy with 16 ounces water and still seemed hungry. Systemic review and family history were noncontributory.

Physical examination showed an irritable, 6-week-old, edematous male infant in no acute distress. Vital signs were normal. Weight was 7 pounds 15 ounces. Except for a diffuse papular rash, physical examination was normal.

Laboratory Data: Hemoglobin was 13.5 grams; erythrocytes, 4.4 million; differential—leukocytes, 13,700; polymorphonuclears 75, lymphocytes 23, monocytes 1, eosinophils 1; blood urea nitrogen 11 mg. per 100 ml.; total serum protein 3.2; albumin 2.0, globulin 1.2; cholesterol 66 mg. per 100 ml. Urine was normal; stool trypsin, normal; duodenal trypsin and amylase, normal. Roentgenograms of chest, normal. Calcium, phosphorus, and alkaline phosphatase were normal.

Course in Hospital: Patient was continued on Mull-Soy for one week, then the formula was changed to evaporated milk and Dextri-Maltose, which the infant took well. He became edema-free in about two weeks, but continued to lose weight over the next five weeks. After eight weeks in the hospital without weight gain an upper respiratory infection developed, for which the infant was treated with steam inhalations, whole blood transfusions, and antibiotics. Shortly after this episode he began to gain weight. Serum proteins were now 6.2 Gm. per 100 ml., albumin 3.8, and globulin 2.4. Throughout the following month the patient ate voraciously but failed to gain. At 6 months of age, four and one-half months after admission, the child was placed on a balance study, and was removed from the study twenty-eight days later. At the start of the collection period he weighed 8 pounds 7 ounces and on completion, 8 pounds 3 ounces. After termination of the balance study, he was continued on human milk for three weeks, during which he started to gain well. His formula was then changed to cow's milk, and he was discharged, weighing 10 pounds.

At 9 months of age the infant was readmitted with laryngotracheobronchitis, at which time he weighed 11 pounds 7 ounces. At the age of 18 months he was again admitted for iron-deficiency anemia; at this time he weighed 22 pounds 4 ounces. The nutritional deficiency responded to conventional treatment; the child appears normal and otherwise healthy, and is taking a full diet. Balance data are summarized in Table V.

On modified cow's milk feedings, this child excreted 52 per cent of the ingested fat in the stool, and 2 per cent of the dietary fat on feedings of human milk. During the course of the study, the infant was in negative

TABLE V. BALANCE DATA ON ILL CHILD R. S. FED MODIFIED COW'S MILK (CM) AND HUMAN MILK (BM)

			DAILY AVERAGES							
DATE 1954	WT.	DIET	URINE VOL.	URINE N (GM./ DA.)	STOOL N (GM./ DA.)	INTAKE N GM./ DA.	AV. DAILY BAL.	STOOL pH	STOOL FAT*	SERUM PROTEIN
7/19	3.84	CM	280	0.90	0.83	1.39		7.0		5.9
7/25	3.52						−.34		52	
8/11	3.66	BM	350	0.81	0.25	1.38		5.5		
8/17	3.72						+.32		2	5.9

*As per cent of dietary fat.

nitrogen balance and lost approximately 50 grams in weight daily while fed on cow's milk. However, on human milk, and approximately the same intake of nitrogen (nearly 400 mg. per kilogram per day), he was maintained in positive nitrogen balance and gained 9 grams daily, regaining most of the weight he had lost during the cow's milk feeding.

DISCUSSION

Block and Bolling[17] studied the amino acid distribution of human and cow's milk. Because of the similarities in amino acid distribution, they suggested that any superiority of protein in human milk "must be based either on differences in the nonprotein amino acid fraction or on teleological reasoning."

In this study a small and statistically insignificant increase in nitrogen retention was observed on human milk feedings. Seven of the nine babies in the series showed increased nitrogen retention when fed human milk. More nitrogen was retained during the cow's milk feeding by Baby 6 who was fed cow's milk at a higher protein level than that of human milk, and by Baby 9, fed human milk at a slightly higher protein level than that of the cow's milk formula.

When the data of Gordon and associates[7] are recalculated, using only periods in which nitrogen intake, whether from human or cow's milk, was almost equal, a similar tendency toward slightly better nitrogen retention occurred on feedings of human milk. Talbot and Gamble[18, 19] have likewise shown earlier nitrogen equilibrium in newborn infants fed human milk than in those fed cow's milk. Recently, Stearns[8] has collected published data, and she concludes that at higher nitrogen intakes, infants fed human milk retain more nitrogen than those fed cow's milk at similar protein intake levels.

The balance calculations in this study were made on total nitrogen intake and total nitrogen excretion. The extent of utilization of urea, ammonia, and other nonprotein, nonamino acid constituents of milk by the human infant is little known. Snyderman and co-workers[20] have recently shown that the human may be able to utilize small amounts of urea in protein synthesis. These constituents account for approximately 20 per cent of the total nitrogen of human milk and 5 per cent of the total nitrogen of cow's milk.[21, 22] If these values are subtracted from the nitrogen intake of the infants in the series, and only the actual protein intake is calculated, the greater retention of nitrogen from human milk becomes statistically significant as compared to the retention from cow's milk.

Balance techniques provide information concerning utilization of foods, although certain limitations are involved. Some of these limitations are related to collection methods in themselves. For example, regurgitation, which in this study was small in amount, is a source of error. Likewise, sweat losses of nitrogen are usually small, hence were not measured in this study.

Another source of error is related to restriction of activity of the infant. Variations in balance of as much as 30 to 40 per cent from the average of the remaining periods were observed in some babies during the initial three-day period following placement on the metabolic frame. These initial periods were discarded after adequate measurements were made subsequently, since it was felt that such differences

were related not only to intake and output, but also to such variable factors as adrenal response. After the first three-day period, the balance data usually were relatively constant as long as the diet remained constant.

This type of variation in the initial three-day period was unpredictable. In some babies the nitrogen excretion for the first three days was higher than in subsequent periods; in others, excretion was lower; and in a few babies, the nitrogen excretion in the first period was similar to that of subsequent periods.

One of the difficulties of a study involving alternation of diets is in determining the point at which the carry-over effect of the preceding diet has ceased. After the infants were placed on the metabolic frame, they were prefed for one week before collection of samples was started. Each time the diet was changed the infants were maintained on the new diet for three days before collections were resumed. The change in stool flora to *L. bifidus* var. *pennsylvanicus* persisted for as long as two weeks after the diet was changed. A longer equilibration period between changes of the diet might have shown greater differences between the two diets studied.

Other methods of determining the biological value of proteins were used. The creatinine:nitrogen ratio, a useful index of biological value in dogs,[23] showed no significant variation between human and cow's milk protein in this study.

Excretion of protein metabolites (urea and ammonia) in the urine, also used for determining completeness of protein utilization,[24] showed no significant variation in this group of babies.

In the course of this study, an attempt was made to keep the infants on a very low protein intake, and in this way exaggerate the differences, if any, in biological value of the two proteins. Babies 5 and 7, on such a diet, retained slightly more nitrogen during feedings of human milk. These retention data, however, are so nearly alike as to suggest no major differences in the biological value of the proteins in the two milks on this basis.

These two infants were fed a diet containing approximately 125 mg. nitrogen per kilogram per day for forty-five and forty days, respectively. During such low protein intake these children were clinically well, remained in positive nitrogen balance, and continued to gain 18 and 10 grams a day, respectively. It is suggested that, at least under the stringent limitations of a balance study, previously estimated minimum nitrogen requirements are high. A similar result was reported by Kaye and associates[25] in a shorter balance study.

The minimum nitrogen requirement of the infant is not definitely known. Allowances are frequently estimated at 300 mg. per kilogram per day[26] to satisfy the requirements for basal metabolism, growth, and activity, an amount two and one-half times that given to the two infants observed.

Patient R. S. is a separate example of a type of food intolerance. He failed to thrive on evaporated milk mixture, Mull-Soy, and diluted cow's milk supplemented with Karo syrup or Dextri-Maltose. When human milk was substituted he gained weight, became alert and happy, and was maintained in positive nitrogen balance. Clinically, human milk seemed life-saving for this child. It seems that there are a few infants who cannot be maintained in positive metabolic balance on substituted formulas, but

who do well on human milk. It is unlikely that this child's case is an example of milk allergy, as he exhibited none of the classical clinical signs, and he showed the same type of intolerance to cow's milk protein as to soybean protein.

The human milk eluate in this study has increased growth and nitrogen retention in rats.[6] As previously noted, this eluate supports the growth of *L. bifidus* var. *pennsylvanicus* in vitro. No effect on growth or on nitrogen retention was demonstrated in the babies fed the dilute cow's milk formula supplemented with human milk eluate. However, at the same time a slight, but definite shift to more acid pH in the feces was noted.

The effect of this factor on the pH of the stools indicates that human milk eluate added to dilute cow's milk formulas may alter the infant's intestinal flora. The consistent decrease in nitrogen retention after the withdrawal of milk eluate supplements may also indicate a significant biological effect.

The rat requires a much higher protein intake to maintain growth than does the human being. The diet used in the previous study on rats was similar in composition to that used in this series. Therefore, the diet fed to the rats was relatively more deficient than that fed to the human subjects. It is possible that in the presence of a deficient diet, with depletion of protein stores, an anabolic effect of the bifidus factor of human milk might be similarly demonstrated in babies.

SUMMARY

Nitrogen balance data on nine healthy infants indicate that nitrogen is slightly better retained from human than from cow's milk when both milks are fed at equiprotein and equicaloric levels. If correction is made for increased urea in human milk, the greater retention of nitrogen during feeding of human milk is of statistical significance. The increased nitrogen retention is apparently the result of better absorption of protein rather than of differences in metabolism of protein.

Nitrogen balance studies of short duration may be misleading because of differences not associated with intake and output alone.

Certain infants remained in positive nitrogen balance on feedings of 125 mg. nitrogen per kilogram per day, regardless of whether the source of the protein was human or cow's milk. This indicates that the protein of human and of cow's milk is approximately equal in biological value, and that infants may remain in positive nitrogen balance and grow satisfactorily on feedings of 0.8 Gm. protein per kilogram per day.

One infant failed to thrive and could not be maintained in positive nitrogen balance except on human milk feeding.

The superiority of human milk over cow's milk as an infant feeding is probably not related to superior biological value of the protein of human milk.

The bacterial flora of the intestine, as determined by stool cultures, differs on feeding of human and of dilute cow's milk. A much greater proportion of the *L. bifidus* organisms present in the stools of babies fed human milk are of the variety "pennsylvanicus" than are those in the stools of infants fed cow's milk.

A biological effect on the intestinal flora of the crude bifidus factor, as

shown by a decrease in stool pH, is detectable in infants.

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EFFECT OF LACTOSE ON NITROGEN METABOLISM AND PHENOL EXCRETION IN INFANTS

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RETENTION of protein by the infant is related to the biological value of the protein in the diet, the adequacy of the intestinal tract, and other factors.

Duncan[1] has summarized, in an excellent review, present knowledge of the physiological effects of lactose. These effects include increased calcium absorption, aciduric intestinal flora with predominance of *Lactobacillus bifidus*, and alterations in absorption of fats, vitamins, and other carbohydrates. Duncan states that lactose in the diet "produces healthy, firm-fleshed babies with few gastrointestinal upsets."

The effect of dietary lactose on protein metabolism is unknown. In the classic study by Gordon and associates[2] on nitrogen retention by premature infants, human milk, which contains lactose as the only carbohydrate, was compared with skimmed cow's milk fortified with Dextri-Maltose and olive oil or calcium paracaseinate. When these two milk formulas were fed at equiprotein, equicaloric levels, nitrogen retention was approximately the same.

Metabolic products of protein metabolism include urea, ammonia, amino acids, and polypeptides. Breakdown products of the aromatic amino acids include phenols and phenolic compounds. It might be expected that changes in food composition would alter urinary phenol excretion, either through change in intestinal flora or differences in intermediary protein metabolism.

Phenols are normally excreted in small amounts in human urine or may be found in increased quantities in patients with phenyl ketonuria[3] and following ingestion of certain phenolic toxic agents. Phenols are mainly detectable in the urine as metabolic products of tryptophane and tyrosine metabolism,[4] or as absorption products of intestinal putrefaction.[5] Levine and co-workers[6] have noted the excretion of *p*-hydroxyphenyllactic and *p*-hydroxyphenylpyruvic acids in the urine of premature infants fed tyrosine and phenylalanine. These phenolic acids decreased in the urine of the infants after administration of ascorbic acid or after decreasing the protein intake.

In large quantities, free phenols are toxic. Less is known of the significance of the phenolic acids. Phenols are usually detoxified in the liver. Detoxification products include glucuronides, sulfates, and combinations with glycine.

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The present study was designed to determine protein retention after feeding commonly used infant formulas. The chief difference between the formulas lay in the presence of lactose or Dextri-Maltose as the source of carbohydrate.

METHOD

Five healthy male infants were selected from the nursery of a large general hospital* and placed on balance studies. They had not previously been breast fed nor had they received antibiotics.

Two concentrated, sterilized liquid formulas were prepared as follows:

1. Lactose Formula†	
Cow's milk protein	1.5%
Blend of vegetable and animal fats	3.5%
Lactose	7.0%
2. D.M. Formula‡	
Cow's milk protein	1.5%
Butterfat	3.6%
Dextri-Maltose No. 1	4.8% (to make total carbohydrate 6.8%)

In the foreperiod of seven days, the lactose formula was fed.

The lactose formula was then fed to each of the babies for a period of twelve to twenty days, followed by the Dextri-Maltose formula for a similar period, after which the lactose formula was reinstituted for the third period of the study. All babies were given daily supplements of oral multiple vitamin drops. The ages of the babies and length of feeding periods are shown in Table I.

*Philadelphia General Hospital.

†Lactose formula (S-M-A, food formula for infants) kindly furnished by Wyeth Laboratories.

‡D.M. formula prepared from available ingredients in a manner similar to S-M-A by Wyeth Laboratories.

A 1-month-old baby was fed frozen and reheated human milk containing 1.1 per cent protein, and a diluted cow's milk formula containing 1.1 per cent protein, 7 per cent lactose, and 3.2 per cent fat. Phenol excretions were determined during these feedings.

The total excretions of urine and of stools were collected. The techniques of preparation of urine and stools and methods of analysis for the nitrogen components were similar to those described in a previous study.[7]

Excretion of phenolic compounds in the urine was determined by a method essentially similar to that described by Bray and Thorpe[8] and by Rogers and associates.[9]

Ten cubic centimeters of urine was brought to pH 8 with 2 per cent NaOH and saturated with NaCl. The urine was placed in separatory funnels in an automatic shaker and extracted three times with 25 c.c. ether for ten minutes. Ten milliliters of water was added to the combined extracts, and the ether carefully evaporated. One milliliter of the aqueous residue was diluted to 10 ml. with water, and 1 ml. Folin-Ciocalteau reagent and 2 ml. of 2 per cent sodium carbonate were added; the blue color developed by the ether-extractable phenols at pH 8 was read in a photoelectric colorimeter with a red filter in comparison with phenol as a standard.

The urine in the separatory funnel was then brought to pH 1 with 10 N H_2SO_4, and immediately extracted in the same way. The color was developed and read in a similar manner. The standard used was *p*-hydroxyphenylacetic acid.

TABLE I. BALANCE DATA

BABY NO.	AGE (DA.)	BIRTH WT. (KG.)	WT.*	DAYS ON DIET	AVG. WT. GAIN (GM./DAY)	FORMULA	N† INTAKE GM.	N† URINE GM.	N† STOOLS GM.	TOTAL BAL.	% RETENTION
1.	28	3.18	3.54	15	21	I	19.94	11.65	3.70	4.59	23
			3.85	24	19	II	32.03	20.26	7.69	4.08	13
			4.30	18	7	I	23.88	16.25	4.35	3.28	14
			4.55								
2.	31	3.20	3.50	15	12	I	19.40	10.52	5.03	3.85	20
			3.68	18	26	II	23.96	14.26	5.72	3.98	16
			4.15	18	14	I	19.87	13.46	3.47	2.94	15
			4.40								
3.	17	3.56	3.63	15	12	I	19.25	5.76	3.05	10.44	54
			3.81	15	18	II	19.04	6.95	2.84	9.25	49
			4.08	15	13	I	19.73	9.37	4.23	6.13	32
			4.28								
4.	17	2.45	2.53	15	19	I	17.85	4.77	4.36	8.72	49
			2.82	12	12	II	12.81	4.72	2.00	6.09	47
			2.96	18	6	I	19.91	9.62	2.63	7.66	39
			3.07								
5.	24	3.20	3.40	15	18	I	18.67	8.13	3.30	7.24	39
			3.67	15	13	II	18.50	8.98	3.15	6.37	35
			3.87	15	14	I	18.78	8.50	2.58	7.60	41
			3.98								
Daily					16	I	1.27	0.53	0.26	0.48	38
aver-					18	II	1.27	0.64	0.24	0.39	31
age					11	I	1.22	0.68	0.21	0.33	28

*Weight in kilograms. First three weights for each baby were determined at the start of each new feeding period. The fourth weight represents the weight at the conclusion of the last feeding period.

†Total nitrogen for the total number of days of the study on each formula.

TABLE II. PHENOL EXCRETION AND STOOL pH

BABY NO.	FORMULA	PHENOLS MG./DAY*				CREATININE MILLIMOLES /DAY	PHENOL × 10/Cr				STOOL pH
		FREE†	ACID‡	CONJ.§	TOTAL		FREE†	ACID‡	CONJ.§	TOTAL	
1.	I	3.3	7.2	3.8	14.3	4.5	7.3	16.0	8.5	31.8	5.1
	II	6.0	14.9	6.3	27.2	6.9	8.7	21.6	9.1	39.4	6.8
	I	3.7	11.9	4.8	21.4	7.1	5.2	16.8	6.8	28.8	7.0
2.	I	9.2	7.2	3.2	19.6	4.9	19.2	15.0	6.7	40.9	4.2
	II	5.7	11.4	3.6	20.7	5.1	11.2	22.4	7.1	40.7	6.5
	I	3.6	8.1	2.3	14.0	5.7	6.3	14.2	4.0	24.5	6.4
3.	I	3.1	7.3	2.8	13.2	6.6	4.7	11.1	4.2	20.0	5.9
	II	3.7	9.0	3.4	16.1	5.0	7.4	18.0	6.8	32.2	6.4
	I	6.2	11.8	2.1	20.1	4.2	14.8	28.0	5.0	47.8	6.0
4.	I	4.6	10.0	1.7	16.3	3.9	11.8	25.6	4.4	41.8	5.4
	II	5.7	20.1	3.5	29.3	4.6	12.4	43.8	7.6	63.8	6.2
	I	6.1	17.6	5.1	28.8	5.3	11.5	33.2	9.6	54.3	6.0
5.	I	6.9	9.9	2.5	19.3	4.4	15.7	22.5	5.7	43.9	5.4
	II	8.7	17.4	2.9	29.0	5.4	16.1	32.3	5.4	53.8	6.5
	I	10.1	15.5	3.8	29.4	5.8	17.4	26.7	6.4	50.5	
Daily	I	5.4	8.3	2.8	16.5	4.8	11.3	17.3	5.8	34.4	5.2
aver-	II	6.0	14.5	3.9	24.4	5.4	11.3	26.9	7.2	45.2	6.5
age	I	5.9	13.0	3.6	22.5	5.6	10.5	23.2	6.4	40.2	6.3

*Expressed as mg. *p*-hydroxyphenylacetic acid.

†Extractable at pH 8.

‡Extractable at pH 1.

§Conjugated phenols after hydrolysis with H_2SO_4, extracted at pH 8.

Conjugated phenols were determined after hydrolysis. The urine in the separatory funnel was transferred to a flask, an equal volume of 10 N H_2SO_4 was added, and the mixture boiled under reflux for one hour. The urine was adjusted to pH 8 and re-extracted as for free phenol. The color was developed and read as before.

RESULTS

Total nitrogen intake, excretion, and balance are shown in Table I. Daily nitrogen intake was approximately constant and averaged 1.27 Gm. for the first feeding of the lactose formula, 1.27 Gm. for the D.M. formula, and 1.22 Gm. for the last feeding of the lactose formula. Nitrogen retention averaged 38 per cent for the first feeding of the lactose formula, 31 per cent for the D.M. formula, and 28 per cent for the last feeding of the lactose formula.

All of the babies retained more nitrogen during the initial feeding of lactose formula. In three of the five babies, retention was greater in the second period (D.M. formula) than in the third period (lactose formula).

Excretion of phenols and phenolic products is shown in Table II. The average total phenolic excretion was highest after feeding D.M. formula, averaging 24.4 mg., as compared to 16.5 and 22.5 mg. after feeding lactose formula in the first and third periods, respectively. The most marked differences were noted in the phenolic compounds extractable at pH 1. Excretion of this fraction of phenolic compounds was higher in all except one of the feedings of the D.M. formula.

For comparison, stool pH is listed in the last column of Table II. In general, the lower the stool pH, the lower the phenol excretion.

The average daily excretion of phenols, expressed as *p*-hydroxyphenylacetic acid, during the lactose formula, was: free phenols—(free) 5.6 mg.; phenolic compounds extracted at pH 1 (pH 1), 10.6 mg.; conjugated phenols (conjugated), 3.2 mg.; total phenols (total), 19.4 mg.; and during the D.M. formula: free, 6.0 mg.; pH 1, 14.5 mg., conjugated, 3.9 mg., total 24.4 mg.

The average daily excretion of phenolic compounds by the 1-month-old baby fed human milk with 1.1 per cent protein was: free, 5.0 mg.; pH 1, 11.1; conjugated 2.7, total 18.8; and for this baby during the feeding of the cow's milk formula containing 1.1 per cent protein and 7 per cent lactose: free 4.0 mg., pH 1, 8.2 mg., conjugated 1.6 mg., total 13.8 mg.

DISCUSSION

The ingredients of most widely used infant formulas include cow's milk, carbohydrate, and water. Two of the carbohydrates in common use are lactose, the natural sugar in all mammalian milks, and a mixture of maltose and dextrins obtained by incomplete starch hydrolysis.

It has been known for a long time that lactose is absorbed from the intestine in a manner different from the absorption of other sugars. Intestinal flora also have been changed when another carbohydrate is substituted for lactose in infant feeding, *Lactobacillus bifidus* being better maintained when lactose is fed. Calcium

and magnesium absorption are increased when feedings contain lactose. It is said that the body tissue of babies fed lactose contains less fat than does the tissue of those fed other sugars. It also has been postulated that galactose has a role in the formation of cerebrosides. These and other effects of lactose in the human organism have been documented by Duncan.[1]

Since excreted phenols partly represent "bacterial putrefaction of aromatic amino acids in the intestine,"[5] it was expected that a change of intestinal flora would alter phenol excretion. Aterman[10] and Rogers and their associates[9] have shown such a change with antibiotics.

The results of this study indicate that phenolic excretion, especially of the phenolic acids, is higher when Dextri-Maltose is substituted for lactose in infant feeding. Since this study was designed to measure phenolic excretion in infants fed two commonly used formulas, the lactose was included in the formula which contained a mixture of animal and vegetable fats, and the Dextri-Maltose was used in the formula which contained butterfat and some lactose. It would be expected that the fat would contribute little to the phenol excretion, but it cannot be stated that Dextri-Maltose alone was responsible for the increase in phenol excretion.

The data indicating increase in phenolic excretion by infants fed the formula containing Dextri-Maltose are too scant to permit statistical analysis. The increase occurred in all babies when the lactose formula was followed by the Dextri-Maltose formula. Since, after reinstitution of the lactose formula, the pH of the stools did not usually return immediately to the average observed during the initial period, it might be expected that longer collection periods might have permitted a more significant change in phenolic excretion.

Nitrogen retention was 5 to 10 per cent greater in all babies fed the lactose formula, whereas the nitrogen intake was constant on both formulas. Following feeding of the Dextri-Maltose-containing formula, three of the five babies showed decreased nitrogen retention when the lactose formula was reinstituted. Since phenol excretion is related to protein metabolism, it would be expected that anything that increases excretion of phenol would lower nitrogen retention.

In spite of Volterra's[11] comment that nitrogen intake in adults does not affect phenolic excretion, our unpublished data in infants and the data of Levine and co-workers[6] indicate that phenolic excretion may increase with increase in nitrogen intake. However, both formulas used in the present study contained protein in equal amounts, similar to the protein content of human milk (1.5 per cent, or slightly less than one-half that of cow's milk).

The identity of the phenols and phenolic acids is unknown. Whether the levels of phenols or phenolic acids in urine have any physiological significance is also unknown. The data in this paper indicate a free phenol excretion in infants of 3 to 10 mg. a day, compared with 11 to 70 mg. a day in adults.[12] Hydroxy acids excreted by the infants amounted to 7 to 20 mg., as compared to an excretion of 49 to 80 mg. by adults.[12] Excretion of phenols by the one infant

fed human milk was somewhat lower than the average for babies fed either cow's milk formula.

Even if phenolic excretion, per se, is not an indication of a circulating toxic metabolite, it seems likely that excessive phenolic excretion, like excessive nitrogen or water excretion, may represent a potential overloading of the excretory mechanism of the young infant.

SUMMARY

Phenolic excretion was measured in five infants fed variations of common infant formulas. The main difference in the formulas was in substitution of Dextri-Maltose for part of the lactose in one feeding mixture. The nitrogen content was the same in type and quantity.

Nitrogen retention was greater in the infants fed the lactose-containing formula.

The infants tended to excrete more phenols during feeding of the formula containing Dextri-Maltose than during feeding periods on the formula containing lactose as the sole carbohydrate. Excretion of phenolic acids was much greater in the infants fed the formula containing Dextri-Maltose. The nature and significance of these phenolic acids are unknown.

The range of normal phenolic acid excretion for infants is presented.

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SERUM AKERFELDT TEST FOR SCHIZOPHRENIA IN CHILDREN

Preliminary Report

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In 1955 Akerfeldt,[1] in Sweden, began studying changes in serum of patients with various mental disorders. In these patients, he found that N,N-dimethyl-para-phenylenediamine hydrochloride was oxidized, usually within five minutes, so that the normal yellow color of serum was changed to varying shades of red. In normal persons the change took longer and gave a lighter red tint. Akerfeldt tested the blood serum of 300 patients with schizophrenia and found a positive reaction in 80 per cent.[2]

The purpose of this study was to determine the specificity of the reaction on a group of hospitalized nonpsychotic children, and on two identical twins with autism or childhood schizophrenia.

METHODS AND MATERIALS

The test was performed on 150 consecutive unselected sera sent to the Pediatric Chemistry Laboratory. All sera were allowed to stand for several hours in order to permit degradation of ascorbic acid. The serum was collected under oil to avoid oxidation by air. One cubic centimeter of a 0.1 per cent solution of N,N-dimethyl-para-phenylenediamine monohydrochloride* was added to 1 c.c. of serum. No buffer was used. Color reaction was read by visual inspection at 5 minutes and recorded as positive (pink to red) or negative or doubtful (either no change in the normal yellow color of serum or a change to pale pink).

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*Eastman Kodak Chemical MW 172.66.

RESULTS

Of the 150 sera tested, there were 45 positives (30 per cent), 5 doubtfuls (3 per cent) and 100 negatives (67 per cent). The clinical diagnoses of the positive reactors were varied and included pneumonia, nephrosis, asthma, mental retardation, congenital heart disease, and two patients with no clinical organic disease. The 150 children ranged in age from 6 months to 14 years. Preliminary analysis of the data revealed no clear-cut differences in age, sex, or clinical diagnoses between the children with positive and those with negative reactions.

The sera of two female identical twins, 2½ years of age, with childhood schizophrenia gave positive reactions.

DISCUSSION

Akerfeldt found positive reactions in 80 per cent of patients with schizophrenia. He also noted a smaller but significant number of positive reactions in patients with rheumatoid arthritis, pregnancy, hepatitis, and malignant carcinoma. This work has recently

been confirmed in this country. Abood[3] reported the results of the Akerfeldt test performed on the sera of over 1,000 patients. Para-phenylenediamine was used instead of N,N-dimethyl-para-phenylenediamine hydrochloride. He found positive reactions in 81 per cent of patients with acute schizophrenia, and only 3 per cent positive in normal controls. As in Akerfeldt's work, Abood noted positive reactions in other groups; 72 per cent in pregnant women; 41 per cent in patients with malignant carcinoma; and 28 per cent in children with severe mental retardation. In our study two patients with childhood schizophrenia had positive reactions as did 30 per cent of 150 unselected, hospitalized children with various other disorders.

The two substances which are believed to be concerned in the positive reaction of the Akerfeldt test are the copper-containing enzyme ceruloplasmin,[4] an oxidase, and ascorbic acid. Cartwright and associates[5] have reported elevation of ceruloplasmin in patients with schizophrenia. Leach and co-workers[6] have indicated that the ceruloplasmin extracted from patients with schizophrenia is qualitatively different from that obtained from normal individuals.

It has long been considered that an inborn error of metabolism may exist in the functional psychoses. Hoffer and associates[7] have postulated that an abnormal metabolism of epinephrine and nor-epinephrine, with production of metabolites such as adrenochrome, a degradation product, may play a role in the etiology of schizophrenia. Adrenochrome is an indole-containing compound which has been shown to be capable of producing schizophrenia-like states.[8]

Leach and Heath[9] have reported an increased speed of epinephrine oxidation in patients with schizophrenia. In turn, speed of oxidation is proportionate to the amount of ceruloplasmin present.[10] Thus there may be an elevation of ceruloplasmin in patients with schizophrenia and other disorders, and this may be the factor producing a positive reaction in the Akerfeldt test.

SUMMARY

1. A modified Akerfeldt test was done on the sera of 150 unselected hospitalized children. There were 45 positives (30 per cent), 5 doubtfuls (3 per cent), and 100 negatives (67 per cent).

2. The sera of two female identical twins with childhood schizophrenia gave positive reactions.

3. The factors which may be concerned in the positive reactions are briefly discussed.

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On Cutting the Tongue

This is an operation so simple and so easily executed that no mother need to hesitate a moment about performing it herself, as I have done for several of my children with perfect safety and success; by taking a pair of very sharp scissors and holding them between her fingers very near the points, so as to preclude the possibility of cutting more than the very outward edge of the string that confines the tongue, and thus avoid all danger of cutting too far, or wounding any of the veins beneath the tongue; from which it is said infants have sometimes bled to death. Another danger arising from this operation is said to be *suffocation*, from the child's swallowing the point of its tongue and which is owing to cutting *too much* of the string or bridle; but I can truly say that although there may be danger of one or both these dreadful consequences, yet I verily believe any judicious mother may perform the operation without the least apprehension, provided she feels sufficient resolution: otherwise she had better employ some professional gentleman to do it. My babe, who is now in arms, had his tongue tied to the very end, so that whenever he cried or attempted to lift his tongue it was drawn into the form of a heart. As soon as I was able to attend to him, I seized an opportunity when he was asleep on my lap; and, gently placing the fingers of my left hand under the tongue, I took a pair of nice scissors, and in the manner above directed with ease severed so much of the string as allowed him to suck with freedom and the babe never awoke or appeared to feel it in the least: but I soon found the operation was not complete enough to permit the tongue to move as it ought to do; and when he was two months old, fearful lest it might cause some impediment in his speech, I cut the string a little more, and although the child was then awake, he never showed the least uneasiness by which I could suppose it caused him any pain; but smiled the whole time. His tongue bled a very little and ever since has appeared perfectly free.

THE MATERNAL PHYSICIAN, NEW YORK, 1811.

THE MANAGEMENT OF HYPERTROPHIC PYLORIC STENOSIS IN A COMMUNITY HOSPITAL

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ONE of the problems which confront thoughtful physicians in any hospital is to decide which types of patients can be safely cared for in the local hospital and which should be transferred to some other institution where particular skills, specialized facilities, or both are available. Nowhere is this problem more keenly felt than in community hospitals which are within easy commuting distance of metropolitan medical centers, and in no branch of medicine or surgery is the problem in sharper focus than it is in dealing with the specialized problems of children. The natural desire of the parents is to have children treated in the home community where they can be visited regularly and easily, where the expenses are perhaps less than in a large city, and where follow-up care is no problem because of the availability of the family doctor and the surgeon.

Straightforward problems, such as hernia and hydrocele, usually are treated locally by any competent surgeon whether or not he has had any particular training in children's surgery. The same is true of urgent problems such as appendicitis and intussusception. Complex and nonemergency situations, such as Hirschsprung's disease and atresias of the esophagus or intestine, are seen only once or twice each year in a community surgical practice and there is no question but that these problems are better handled by transfer to one of the pediatric centers in the metropolitan area. The same is true of congenital defects, such as harelip, which are not an immediate threat to life but which require the artistry and skill of a highly trained plastic surgeon.

Somewhere on this sliding scale of problems specific to infants lies congenital hypertrophic pyloric stenosis. This disease of young infants is serious if not treated surgically, although on occasion there are patients who recover spontaneously or after careful medical management. The technical surgical maneuvers are not complicated but must be carried out precisely to avoid inadequate separation of the pyloric muscle fibers or an unrecognized perforation of the mucosa, particularly at the duodenal end. Furthermore, because of the insidious onset of the symptoms of pyloric stenosis there are few conditions in which the surgeon's success is so dependent on the diagnostic acumen of family physicians and pediatricians. The two latter groups are the ones who make the diagnosis and refer the patient to a surgeon early enough so that the operation is now usually carried out in well-nourished and well-hydrated babies. These babies are a far cry from the marasmic,

From the Burbank Hospital.

sometimes nearly moribund children that in former years were turned over to the surgeon after prolonged and futile experimentations with diet and antispasmodics. The operation for pyloric stenosis has been a completely standardized procedure for over forty years. The steady and continuing drop in the mortality of this disease, to a level which now approaches zero, is a tribute to family doctors and pediatricians far more than to surgeons and anesthesiologists. Finally, one must give credit to the nursing profession because without available nurses experienced in dealing with infants the disease could continue to carry a substantial mortality rate.

These were the thoughts that made us review the records of infants with pyloric stenosis at the Burbank Hospital in Fitchburg, for the period from May, 1949, through May, 1956. Fitchburg, only fifty miles from Boston, is a community of 43,000 people drawing medical problems from a population of perhaps 55,000. During the seven years under consideration an average of over 1,100 babies was born each year in the Burbank Hospital. During this time the diagnosis of pyloric stenosis was made thirty times, approximately once for every 270 deliveries.

Before 1949 the hospital did not have a separate pediatric service and all patients in whom the diagnosis of pyloric stenosis was suspected were transferred to one of the Boston hospitals. Exact records for the decade preceding 1949 are not available, but in at least one instance an infant was transferred to a Boston center after prolonged delay and later died following surgery. In the seven years since 1949 thirty cases of pyloric stenosis were diagnosed, and the diagnosis was confirmed at operation in each instance. Six were transferred to one of the metropolitan centers, while twenty-four infants were operated upon locally. The operations were performed by four different surgeons of whom only one had received part of his training on a pediatric surgical service.

Of the six transferred to Boston three were sent at the insistence of the parents rather than because any particular problem was involved in their diagnosis or condition. These three were members of two generations of the same family which had an unusual number of congenital difficulties. Prior to 1949 one member of this family had been treated for hydrocephalus, another for spina bifida and meningocele, and two others for pyloric stenosis. All of these had been treated at a metropolitan pediatric center and, though only one of these four had survived, when three younger members of the same family developed pyloric stenosis, it was understandable that the family desired treatment at the same institution. All three of these younger infants did extremely well despite the fact that one of them was a premature infant weighing less than 3 pounds when the diagnosis was made before transfer to Boston for surgery. The fourth child, in good condition, was sent to Boston by his family physician and did well. This was shortly after the first cases were done locally, and it was the continuing practice of the physician in question to refer any serious problems involving infants to Boston.

There were, however, two infants who presented such serious problems

that, after careful consideration and consultation between the pediatrician and surgeon, they were transferred to the Children's Medical Center.

Case 1 (A38696).—A 7-week-old male infant had vomited continuously after breast feeding had been discontinued at the age of 4 weeks. The infant had lost over 2 pounds of weight, was extremely emaciated and dehydrated, and was critically ill and in need of every possible supportive measure to prepare him for surgery. The patient did well following operation.

Case 2 (A77149).—A 6-week-old male infant had had projectile vomiting for one week. A typical pyloric tumor could be palpated. The complicating factor was the presence of considerable blood in his stools. He had a prolonged bleeding time, and the mother had a history of thrombocytopenic purpura. The child was transferred to the Children's Medical Center, where in addition to pyloric stenosis the diagnosis of pseudohemophilia was made. The bleeding time was controlled with the help of ACTH, and a few days later a successful pyloromyotomy was performed. The child did well following this procedure. The problem of abnormal bleeding has persisted, however. At the age of 4 years he was seen again because of prolonged and extensive bleeding from a minor laceration of his tongue.

Thus of the six patients transferred to Boston four could have been taken care of locally, but the other two needed transfer to a pediatric center because of the severity and complexity of their conditions. If similar problems occurred today such infants would still be transferred to Boston. For complex and difficult problems the importance of the teaching centers cannot be overemphasized. The role of the teaching centers in the routine care of uncomplicated problems referred from outside communities will probably decrease as the general level of medical and surgical care in these communities gradually improves.

Twenty-four infants were operated upon locally. There were no fatalities in this group. Since the operation is never an emergency a short period of time was spent to get each infant into an optimal state of hydration prior to surgery. In most of these patients the diagnosis was made early enough so that all that was necessary was a clysis to overcome the minor degree of dehydration that existed. A few needed more extensive fluid replacement and in only one instance was a preoperative blood transfusion necessary.

A small soft rubber catheter was always passed into the stomach and placed on suction to remove the possibility of vomiting and aspiration of stomach contents during anesthesia and surgery.

A gridiron, subcostal muscle-splitting incision, as described by Robertson, was used in all cases. The skin was closed with subcuticular stitches. In four cases it was necessary to extend the incision somewhat across the rectus sheath to afford more room. Open-drop ether anesthesia was used in all operations. There were no wound complications. The routine postoperative care consisted of small feedings, starting as soon as the babies had completely recovered from anesthesia, and the amount of these feedings was gradually increased so that by the second postoperative day the babies could get along without parenteral supplements. Occasionally postoperative vomiting for a day or so necessitated a slower increase in

this schedule, and in these babies parenteral supplementation was continued to ensure adequate fluid intake. The infants usually went home on the fourth day following surgery.

Technical difficulties were encountered in three patients. Twice the duodenum was opened in the course of the operation. The mucosal defect was recognized and closed in each case. The convalescence was in no way prolonged, and these complications were not considered serious.

In one infant, however, the incision was placed much too low in the abdomen. The tumor was never properly exposed at the duodenal end and the infant continued to vomit postoperatively. On the third day following surgery he was transferred to the Children's Medical Center where he was re-explored, and it was ascertained that the muscle fibers had not been completely separated at the previous operation. In the subsequent operation an adequate procedure was carried out and the infant did well. In this case the surgeon realized during the original procedure that the operation might not be successful. In another instance, although the surgeon was quite satisfied with his operation, the infant did almost the same thing in that he continued to vomit about every other feeding after surgery, and on the fourth postoperative day was transferred to the Boston Floating Hospital. There the infant did not vomit again, took his formula well, and started to gain weight. After three days of observation he was sent home without anything further having to be done. In retrospect, this represented merely an exaggeration of the vomiting which occasionally occurs on the first day or two postoperatively.

The second serious complication was in an infant who received a blood transfusion immediately before the operation. Inadvertently the flow of fluid was not cut off and during the operation the child received about 100 c.c. of saline solution intravenously, went into a state of acute pulmonary edema, and was critically ill for an hour or two. The response to tracheal aspiration and controlled respirations with the anesthesia machine was prompt and by the next day the patient was well.

Thus there were two major complications in this series, the first, the result of incomplete surgery, and the second, the result of overenthusiastic infusion of blood and saline. Fortunately there was a happy outcome in each case.

SUMMARY AND CONCLUSION

The course of thirty patients with congenital hypertrophic pyloric stenosis seen in a community hospital over a seven-year period is discussed. Six patients were transferred to one of the metropolitan pediatric centers, four for the convenience of the patient's family and two for reasons of medical judgment. Twenty-four patients where operated upon locally without mortality. There were two serious complications, one resulting from poor technique and the other from poor judgment.

This study shows that infants with pyloric stenosis can be treated successfully in a community hospital. However, unless a surgeon whose training has included experience at a pediatric center is available, the pediatrician must assume the responsibility not only for the diagnosis, but also for deciding whether an infant with

pyloric stenosis should undergo surgery locally or be transferred to a metropolitan center. He should ask himself with every patient: "Is the infant's best interest served if the operation is performed at the local hospital?" Only if his mature judgment permits an affirmative answer is he justified in proceeding with arrangements for surgery in the community hospital. Under such circumstances, he also must assume the responsibility for pre- and postoperative care. A clinical laboratory capable of helping him guide the fluid and electrolyte therapy, if the need for such guidance becomes necessary, must be available.

It needs re-emphasizing that the surgical maneuvers are less significant than are the prerequisites of early and proper diagnosis, the availability of adequate pre- and postoperative care, competent anesthesia, and reliable nursing care. Only if all these requirements are met may the team of surgeon and pediatrician feel that they can take the joint responsibility for the management of infants with pyloric stenosis in the community hospital.

Joseph Somes, age 9 yrs, died September 5, 1780. "He had eaten too many wild cherries and sweet apples the day before which occasioned his death suddenly."

GLOUCESTER, MASS., VITAL RECORDS.

BCG VACCINATION IN VIRGINIA

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WHILE BCG vaccination has been carried out on a large scale throughout much of the world, its use in the United States has been limited. A small study has been in progress at the Medical College of Virginia, in Richmond, for the past seven years. The results of this study are chronicled in the following.

THE STUDY

Those admitted to the study were infants under 6 months of age, taken at random from the Well-Baby Clinic of the Medical College of Virginia, Hospital Division. Before admission to the program, the patients received a 70 mm. chest x-ray and a Mantoux test. Dosage of the Mantoux test was old tuberculin solution, 0.1 mg., during a period of approximately four years and old tuberculin solution, 1 mg., for the remainder of the seven-year period. If both chest x-ray and tuberculin test were negative, the infant was admitted to the study group. Another chest x-ray and tuberculin test were performed after six to twelve weeks, and every six months thereafter.

METHOD OF VACCINATION AND SIDE EFFECTS

BCG vaccination was performed by the multiple puncture method. For the first two years vaccination was effected in the manner advocated by Birkhaug,[1] and during the ensuing five years the Rosenthal[2, 3] technique was in use.

There was no instance of necrosis or untoward reaction at the site of vaccination during the seven-year period. Undoubtedly many of those vaccinated experienced axillary adenitis of some degree, but in only two were the nodes of sufficient size to influence the parents to return to the clinic for follow-up examination. In no instance did suppuration of the axillary nodes occur. This is in sharp contrast to the high incidence of suppurative regional adenitis noted with the intracutaneous method by other workers.[4]

RESULTS

There were 1,533* infants admitted to the study. Of these, 738 received BCG vaccination and 795 served as a control or nonvaccinated group. One of the control patients and three of the vaccinated infants died, but in no instance was tuberculosis the causative agent.

Not one of the 738 vaccinated patients developed clinical tuberculosis.

Of the 795† nonvaccinated patients, 126 (15.8 per cent) were infected with tuberculosis, as evidenced by a positive reaction in the Mantoux test. Of

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This study was aided in part by a grant from the Richmond Tuberculosis Association.

*All statistics as of Oct. 1, 1956.

†Only four patients were admitted to the control group during the period Feb. 15 to Oct. 1, 1956.

these, 111 (14 per cent) were infected before they attained the age of 3 years, and 90 (11.3 per cent) contracted tuberculous infection by the time they reached 2 years of age (Table I).

TABLE I. INFANTS IN CONTROL GROUP OF 795 INFECTED WITH TUBERCULOSIS

AGE	PATIENTS	PERCENTAGE
Less than 2 years	90	11.3
Less than 3 years	111	14.0
Total to date	126	15.8

Review of chest x-rays and fluoroscopic examinations revealed that fifty of those infected showed evidence of primary tuberculous disease, while seventy-six showed no x-ray or fluoroscopic evidence of tuberculosis (Table II).

TABLE II. ROENTGEN-RAY OR FLUOROSCOPIC EVIDENCE OF TUBERCULOSIS IN CONTROL PATIENTS INFECTED WITH TUBERCULOSIS

PATIENTS	NUMBER
With evidence of tuberculosis	50 (40%)
Without evidence of tuberculosis	76
Total	126

Only three of the control infants infected with tuberculosis had more serious disease. One (L. K.) developed tuberculous pneumonia and received isoniazid therapy for six months.[5] Another (M. B.), with tuberculosis of one of the superficial cervical lymph nodes, received isoniazid for four and one-half months and underwent uneventful excision of the affected node.[5] The third (P. V.) showed parenchymal tuberculosis and has received isoniazid for the past four months. There has been no disease progression.

COMMENT

When the program was first instituted, the Mantoux test with old tuberculin solution, 0.1 mg., was employed both in determining eligibility for admission and for follow-up studies. After approximately three years, it was noted that a large number of those receiving BCG vaccination continued to exhibit a negative reaction in the Mantoux test. Rosenthal[6] suggested that the Mantoux test be done with old tuberculin solution, 1 mg., since a positive cutaneous reaction to tuberculin following BCG vaccination is often not elicited by a lesser testing dose. This was done for both vaccinated and nonvaccinated patients for a period of approximately three years.

By this time an unexpectedly large number of nonvaccinated patients had been demonstrated to have a positive reaction in the Mantoux test (old tuberculin solution, 1 mg.). Thereupon decision was made to continue with the Mantoux test, using old tuberculin solution, 1 mg., in determining eligibility for admission to the study and for follow-up examination of those receiving BCG vaccination. However, old tuberculin solution, 0.1 mg., was introduced for use in follow-up examination of the nonvaccinated infants. Those patients who had shown a positive reaction in the Mantoux test using old tuberculin solution, 1 mg., were retested with old tuberculin solution, 0.1 mg. The accuracy of the test was substantiated in all except nineteen instances. Follow-up visits could not be arranged for this number.

Krohn[7] has suggested that even a Mantoux test employing old tuberculin solution, 0.1 mg., may elicit a nonspecific reaction not indicative of tuberculous infection. However, his application of the statistics of Palmer and co-workers[8] to suggest that approximately one-third of those in Virginia showing a positive cutaneous reaction to old tuberculin solution, 0.1

mg., are not infected with tuberculosis seems hardly justified. Palmer's study specifically omits Virginia.

Further, twenty-eight patients were randomly selected from those 107 infants who showed a positive reaction in the Mantoux test using old tuberculin solution, 0.1 mg. These were retested with old tuberculin solution, 0.01 mg., and twenty-three continued to exhibit a positive reaction, with an average cutaneous reaction of 8 mm. One other showed a questionably positive reaction. (Table III.)

TABLE III. COMPARISON OF POSITIVE CUTANEOUS REACTION IN MANTOUX TESTS WITH OT, 0.01 MG., AND OT, 0.1 MG.

DOSAGE	NUMBER TESTS	POSITIVE	NEGATIVE
OT, 0.1 mg.	28	28	0
OT, 0.01 mg.	28	23	4*

*One doubtful.

While measurements of size of cutaneous reaction are not available for the other patients in this group, another study appears to give some idea as to comparison of degree of reaction in the Mantoux test employing old tuberculin solution, 0.1 mg., and that in which PPD, 0.0001 mg., is used. One hundred thirty-two Mantoux tests were performed on one hundred patients admitted to the United States Public Health Study concerning the efficacy of isoniazid in the prophylaxis against tuberculous meningitis. In each instance, old tuberculin solution, 0.1 mg., was injected into the right forearm and PPD, 0.0001 mg., into the left forearm. From these tests, fifteen negative reactions to old tuberculin solution, 0.1 mg., were noted, and eighteen negative reactions to PPD, 0.0001 mg., resulted. The average size of cutaneous reaction to old tuberculin solution was 11.2 mm. and to PPD, 9.5 mm. It appears, therefore, that PPD, 0.0001 mg., and old tuberculin solution, 0.1 mg., are comparable testing agents as employed in this clinic. (Table IV.)

TABLE IV. SIZE OF CUTANEOUS REACTION IN MANTOUX TESTS (UNITED STATES PUBLIC HEALTH STUDY RE INH IN PROPHYLAXIS AGAINST TUBERCULOUS MENINGITIS)

TEST	OT, 0.1 MG.	PPD, 0.0001 MG.
Number	132	132
Positive	117	114
Negative	15	18
Average size of reaction	11.2 mm.	9.5 mm.

DISCUSSION

The work of Aronson and Aronson,[9] Rosenthal,[10] Heimbeck,[11] and others has demonstrated the value of BCG vaccination. While this procedure has been widely accepted and many millions of people have been so vaccinated, it has not been recommended for general use in this country. In 1949 the American Trudeau Society Statement on BCG[12] recommended its use in the following groups:

1. Those whose occupation causes them to be exposed to tuberculosis, i.e., doctors, medical students, nurses, laboratory workers, hospital personnel, etc.

2. Individuals who are unavoidably exposed to tuberculosis in the home.

3. Patients and employees in mental hospitals, prisons, and other custodial institutions, in whom the incidence of tuberculosis is known to be high.

4. Children and certain adults considered to have inferior resistance and living in communities in which the tuberculosis mortality rate is unusually high.

So far as this particular study is concerned, results are inconclusive.

There were no known deaths from tuberculosis in either the vaccinated or the nonvaccinated group, and only three of the nonvaccinated group developed serious tuberculous disease. Clinical tuberculosis was not noted in the group receiving BCG vaccine.

The material at hand appears to be of greatest value, first, in pointing up the high degree of tuberculous infection among a young age group of clinic patients, predominantly Negro; and, second, in demonstrating the safety of the multiple puncture technique of BCG vaccination with complete absence of either local complications or suppuration of regional lymph nodes.

SUMMARY

One thousand five hundred and thirty-three infants, predominantly Negro, formed the basis for this study. Effectiveness of BCG vaccine was not conclusively demonstrated.

A high degree of tuberculous infection among a group of young clinic patients was noted. Evidence is presented to show that the multiple puncture technique of BCG vaccination is a safe procedure.

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INFANTILE AMAUROTIC FAMILY IDIOCY

A Genetic Approach

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INFANTILE amaurotic familial idiocy, or Tay-Sachs disease, is a genetically determined degenerative disorder of the central nervous system, occurring chiefly in infants of the Hebrew race. Although this disease was described in its classical form in 1887, the intervening years have brought neither effective therapeutic nor adequate prophylactic measures. No ray of hope has ever been offered to the unfortunate parents of these afflicted infants.

A survey of this disease, to evaluate genetic factors upon which logical preventive recommendations could be based, was undertaken by us in New York City. A twelve-year period, 1944 to 1955 inclusive, was chosen for this study. New York City, with 0.3 per cent of the world's inhabitants and 17 per cent of the world's Jewish population, is ideally suited for this purpose. The greatest concentration of patients with this disease should be encountered here, in the city with the largest (2,000,000) Jewish population in the world.

With the cooperation of the Bureau of Vital Statistics of the City of New York, the recorded death certificates for this twelve-year period were analyzed. In this uniformly fatal disease, morbidity and mortality are essentially equal, and a record of deaths over a given period provides an unselected sample of its occurrence. In all except seven cases, the corresponding birth certificates were also located and analyzed.

During the twelve-year period, from 1944 to 1955, fifty-eight cases of infantile amaurotic familial idiocy were reported as the cause of death. The annual incidence of 4.8 cases for New York City is less than usually estimated. The frequency of this disease is probably exaggerated because of the numerous physicians consulted by each patient.

Of the fifty-eight children in this series, thirty-four were males and twenty-four females. The greater frequency in males is not statistically significant. In most previously reported series, no sex predilection was noted.[1] There is no basis for the belief[2] that this illness affects females three times as frequently as males.

The age at death of the children in this series varied from 1 to 5 years, with an arithmetic mean of 27.4 months. In a study completed in 1933, Slome[1] reported 18.6 months as the average span of life. Despite antibiotic and supportive therapy, the course of the disease remains inexorably downhill.

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The age of the father at time of birth varied from 22 to 53, with an average of 33 years. The age of the mother varied between 18 and 41, with an average of 29 years. The countries of origin of the parents are listed in Table I.

TABLE I. COUNTRIES OF ORIGIN OF PARENTS

PARENTS' BIRTHPLACE	FATHER	MOTHER
New York City	21	23
U. S. except New York City	11	13
Russia	7	4
Poland	6	4
Germany	4	4
Austria	1	1
Czechoslovakia	1	1
Hungary	1	1
England	0	1
Unknown	4	4

Among the fifty-eight children, there were two sibling pairs, one of males and one of both sexes.

Originally, infantile amaurotic familial idiocy was described as occurring only among Jews. Our present list includes three cases of apparently non-Jewish antecedents, or 5 per cent of this series. Numerous other cases with no known Jewish ancestry for several generations have been reported from Argentina, Ceylon, China, Japan, Scandinavia, and Uruguay. One Negro infant with this disease was observed in the United States.[3] Slome[1] reviewed 200 cases in the literature and found 135 which yielded relevant information. Of these, eighteen cases could be authenticated as occurring in non-Jewish families, or 14 per cent of the total number. From our figures, the incidence of this disease among Jews in New York City is one per 8,300 births, the annual birth rate for the Jewish population being estimated at 37,500. In terms of total population, the yearly incidence was one per 500,000, half the previously reported figure of one per 250,000. Among non-Jews, the annual incidence was one case per 450,000 births.

In order to estimate the probable accuracy of our figures, we shall list the most likely sources of error. The value of fifty-eight cases per twelve years is undoubtedly the lowest possible figure, since there must have been some cases which were not diagnosed and recorded on death certificates. Two conditions which might falsely inflate the reported incidence were not operative here: (1) As a metropolitan center, New York City may draw patients from other communities; the home addresses of patients' parents in this series, however, were within the city limits. (2) False diagnosis of infantile amaurotic family idiocy is most unlikely, considering the unequivocal character of the clinical picture. The true incidence in New York City, then, is probably somewhat higher than 4.8 per year.

Precise statistical inferences cannot be drawn from so small a sample. On the basis of these figures, there is a possible annual incidence of fifteen cases for the entire United States, seven among Jews and eight among non-Jews. These numbers are presented merely as a mathematical stimulus to dispel the thought that Tay-Sachs disease should not be considered in a non-Jewish infant.

It has long been known that consanguinity plays an important role in the appearance of infantile amaurotic familial idiocy,[4] the frequency of consanguineous marriages having been estimated at 25 per cent.[1, 5] Consanguineous marriages were more common in Eastern than in Western Europe. As inbreeding tends to increase the

incidence of recessive illnesses, consanguinity rates among affected populations and affected families assume considerable importance.

In the past, this disease has been observed more frequently among Russian and Polish than among other Jews. Goldschmidt[6] recently reported from Israel that this disease was ten times as common in Askenazi* than in Sefardi Jews, the incidence being one per 3,000 and one per 30,000 births, respectively. On the other hand, consanguineous marriages were much more frequent among Sefardi than among Askenazi Jews. These findings tend to clarify the problem of the greatly increased "racial" incidence of infantile amaurotic familial idiocy among Jews, despite the fact that Jews make up a cultural group rather than a race. It is not unlikely that this illness arose in Eastern Europe in relatively recent years, and that the genes have since been spreading outward from that focus, in addition to foci elsewhere which have given rise to fewer cases.

We have obtained information on consanguinity from thirty of the fifty-eight families involved. In none of our cases was there any blood relationship between the parents of the affected infants! The absence of the factor of consanguinity in this relatively large series is in marked contrast to previous reports in the literature.[1]

Another unexpected finding was that three of the thirty fathers were physicians. This most likely is a coincidence.

No factors other than familial or racial predisposition have been shown to bear an etiologic relationship to this disease. The bulk of evidence points to a simple recessive type of hereditary transmission for infantile amaurotic familial idiocy. An affected infant is homozygous for the Tay-Sachs gene and, therefore, must have received this gene from each parent. The illness can appear only when two individuals heterozygous with respect to this gene marry, and the chances are one in four that any given child of the couple will have the disease.

By the use of the Hardy-Weinberg equation, the probable incidence of the recessive gene can be calculated.† The number of heterozygote carriers among the Jewish population is estimated as 44,000, or one in about 50, and for non-Jews 18,000, or one in about 300.

This surprising quantitative estimate shows that, in spite of the great rarity of the disease, carriers are by no means infrequent, making up 2 per

*Askenazi Jews are those who come from Eastern and Central Europe, while Sefardis derive from the Mediterranean area.

†If p^2 equals the proportion of affected infants to total births over the same period, then the proportion of heterozygotes in the population is given by $2p(1-p)$. Sibling pairs are counted as one case only, since each set of siblings identifies the same pair of heterozygous parents. For the twelve-year period covered, there were 55 affected Jewish infants, among whom were two sibling pairs. We, therefore, have 53 cases for twelve times the estimated annual rate of 37,500 births.

$$p^2 = \frac{\text{number of cases}}{(\text{annual birth rate})\ (\text{years})} = \frac{53}{37{,}500 \times 12} = 0.0001178$$

$$p = 0.01085$$

$$2p(1-p) = 0.022, \text{ the carrier rate}$$

$$\text{Total number of carriers} = (0.022)\ (2{,}000{,}000) = 44{,}000$$

$$\text{For non-Jews, } p^2 = 3/1{,}350{,}000 = 2.22 \times 10^{-6}$$

$$p = 0.0015$$

$$2p\ (1-p) = 0.003, \text{ carrier rate}$$

$$\text{Total number of carriers} = (0.003)\ (6{,}000{,}000) = 18{,}000$$

cent of Jews and 0.3 per cent of non-Jews. A woman who has had a Tay-Sachs child has demonstrated that she is a carrier of the disease gene. To minimize the probability of occurrence of the illness among her subsequent offspring, artificial insemination may be employed where there is a strong desire for more children. If an unrelated donor of Jewish race is used, the chance of the child having the disease is about 1 in 200; if the donor is not of Jewish extraction, it is reduced to 1 in 1,200. These figures are in good agreement with previous estimates.[7, 8]

The widespread belief that infantile amaurotic familial idiocy first appears at 6 to 8 months is not quite true. The onset may be in utero and the infant is probably born with the disease. Its clinical effects, however, are not manifest for some months. For the same reason, there is no apparent increase in either the stillbirth rate or the prematurity rate[9] in affected families.

The earliest symptoms of infantile amaurotic familial idiocy that we observed were auditory or visual. The former consisted of hyperacusis and the latter of squinting, crossing, and wandering motions of the eyes. Occasionally, marked tremors of the extremities and face were noted even in the newborn nursery and tetany was suspected.

Although these signs are merely suggestive, they serve as an early indication of a central nervous system disturbance and specifically of this illness in a sibling of an affected child.

The symptoms that usually first bring forth the parents' concern are sluggishness and lack of attentiveness. The subsequent clinical picture has been well described and requires no further elaboration. The infant makes little progress in his development. He does not gain in his ability to sit up and, subsequently, loses the physical and mental achievements previously acquired. In the early stages, the muscles are weak and flaccid, whereas in the late stages they are spastic. Ophthalmoscopic examination reveals the most characteristic feature of this disease—a bright cherry-red spot in the center of a white area, occupying the area of the macula lutea.

If the disease is considered only because of the genetic background, funduscopy may reveal the characteristic macular lesion at an early age. We have noted the pathognomonic eye findings in a 3-month-old infant.

The pathology of infantile amaurotic familial idiocy is characterized by the appearance of abnormal cellular lipids in ganglion cells throughout the central nervous system. So far as the retina is concerned, the changes are limited to the nerve cell layer,[10] with thinning-out in the region of the macula and the appearance of phagocyte-like cells loaded with lipoid materials. The ganglion cells in the macula present a markedly abnormal appearance, with loss of Nissl substance, compressed nuclei, and voluminous lipid-filled cytoplasm.[11]

The microscopic picture within the brain is also highly characteristic. The histologic lesions emerge in the neurons of the cerebrum, cerebellum, medulla, spinal cord, and autonomic ganglia[12] and begin, as in the macula, with swelling of the cell body, often of extreme degree, disintegration of the tigroid substance, and simultaneous appearance of fatty substances.[13] These abnormal cellular constituents are held in a different, probably looser,

form by the cellular structure in this illness than in the lipid storage diseases.[14] Inclusion bodies are present, but it is doubtful whether they are an integral part of the pathologic picture of the disease. It has been noted[13] that their presence seems to be associated with convulsive states and myoclonia.

The accumulated fatty substances have recently been demonstrated to represent a new group of lipids, called gangliosides, differing from other cerebrosides by the presence of neuraminic acid.[15] Several types of gangliosides have been identified in the human brain.[16] These lipids normally make up 0.3 per cent of the solids in the infant's brain, while in this illness they rise in concentration to 4 to 8 per cent, partially replacing the cerebrosides.

In view of these findings, the basic defect in infantile amaurotic idiocy has been postulated[17] as a developmental failure in a specific enzyme system, leading to the progressive accumulation of an abnormal by-product of intermediate lipid metabolism. When its concentration passes a threshold level, further central nervous system development is aborted and regression ensues. In accordance with this view, the gross autopsy findings have been shown to be roughly correlated with duration of the illness.[18] There is central nervous system atrophy during the first year, patchy encephalomalacia and meningeal fibrosis during the second, and hydrocephalus thereafter.

This biochemical interpretation deserves our favorable attention. It may well lead to a more positive medical approach. This view goes counter to the customary defeatist belief that since the illness is hereditary, it is by definition incurable. It may lead to efforts to define precisely the nature of the inborn chemical defect and to devise means of counteracting it.

Numerous attempts have been made to detect diagnostic laboratory abnormalities. The electroencephalogram may be abnormal for the patient's age group,[19, 20] recording nonfocal mixed fast and slow dysrhythmias, with signs of asymmetry. The tibial and femoral bone marrow has been shown to be markedly acellular,[21] but without any corresponding alteration in the circulating blood picture. Abnormal lipids were not detected in the aspirated bone marrow or in peripheral blood. Other diagnostic test findings are apparently normal.[22] Recent studies,[23] however, have disclosed some statistically significant, but not pathognomonic, variations from the normal, including elevation of serum neuraminic acid and alpha-2-globulin fraction, with depression of the gamma globulin level in serum and in cerebrospinal fluid. The search for detectable laboratory abnormalities is of great importance, for it offers an approach to the detection of heterozygous carriers and to the consequent control of the disease.

Juvenile amaurotic and infantile amaurotic idiocy do not occur together in the same family. Four to five new cases of the juvenile form occur each year in Sweden. It follows a recessive and monohybrid pattern of heredity. The incidence of consanguineous marriages in this group is approximately 15 per cent.[26]

Two cases of a fulminating lipoidosis, with a full-blown picture at birth strongly resembling infantile amaurotic idiocy, have recently been discovered in the same family.[24, 25] The

detailed findings, however, demonstrate this to be a distinct clinical entity. Among other differences, the nerve cell lipoid is different from that found in Tay-Sachs disease, being insoluble in organic solvents, and extreme microencephaly is present, while Tay-Sachs patients have normal-sized skulls.

GENETIC APPROACH

Once a mother has a child with infantile amaurotic idiocy, the chance of each subsequent sibling having the disease is 25 per cent.[4] Utilization of genetic knowledge provides the most practical prophylactic measures possible at this time.

Sterilization or contraception may be acceptable solutions to some parents. Others may be strongly desirous of having further children if the risk of recurrence can be minimized. Artificial insemination offers such an approach.

Selection of a non-Jewish donor, or a Jew of Sefardic ancestry, for artificial insemination markedly reduces the possibility of further siblings with Tay-Sachs disease.

In preparing for artificial insemination, it is highly desirable to give the father a feeling of importance, participation, and contribution. We advise the following steps: (1) The father himself pays the donor's bill, even though the actual amount may be small or symbolic. (2) He is given active part in the procedure, such as the recording of his wife's temperature to determine ovulation time. (3) The paternal seminal fluid, freed of spermatozoa, is mixed with the donor's semen to provide the injected fluid. (4) The actual injection is done by the father, with the aid of the obstetrician. (5) Legal adoption of infant by parents is resorted to where the law makes it advisable.

In addition to the above safeguards, consent slips are signed by both parents, indicating in clear language that they understand and wish that this procedure be done in order to minimize the chance of illness in their subsequent offspring.

Parents have asked for advice in reference to the future of siblings or first cousins of affected children. Inasmuch as the proportion of carriers of the Tay-Sachs gene is markedly increased among them, their chances of having normal children will be increased if they marry other than Askenazi Jews.

SUMMARY

1. During a twelve-year period, 58 deaths from infantile amaurotic familial idiocy were reported in New York City. The yearly incidence of the disease, in new cases per total births, is one per 8,300 for Jews and one per 450,000 for non-Jews.

2. The average life span in this disease is twenty-seven months and there is no sex predilection.

3. Infantile amaurotic idiocy is transmitted as a recessive trait. The frequency of persons carrying a gene specific for this disease, without presently demonstrable alteration in their physical make-up, is estimated as one in 50 for Jews and one in 300 for non-Jews.

4. Parents of affected infants desirous of having further children can minimize the risk of recurrence by artificial insemination with a suitable

donor. Siblings and cousins of these infants should exercise caution in selection of marriage partners.

5. Recent developments in pathology, particularly in the biochemical field, are reviewed.

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TREATMENT OF ACUTE PURULENT MENINGITIS WITH TETRACYCLINE

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SINCE the introduction of tetracycline in 1953, its therapeutic efficacy has been proved in a variety of infections.[1, 14] Results of careful preliminary trial studies suggested the possible value of this drug in the treatment of acute bacterial meningitis, and during the winter of 1954-1955 nineteen patients admitted to the Los Angeles Childrens Hospital were treated with tetracycline alone. The clinical data in these cases, as well as the serum and cerebrospinal fluid tetracycline levels obtained, are the basis of this report.

MATERIALS AND METHODS

Nineteen children, ranging in age from 2 months to 8 years, with acute bacterial meningitis, were studied. There were thirteen boys and six girls; eighteen children were Caucasians and one was a Negro. The onset of symptoms varied from a few hours to two weeks prior to admission, and 60 per cent had received antibiotics during the period preceding their admission to the hospital. The initial cerebrospinal fluid analysis showed cell counts ranging from 21 to 12,900 cells per cubic millimeter, with polymorphonuclear preponderance and elevated protein and decreased glucose content. The cerebrospinal fluid cultures yielded *Hemophilus influenzae*, type B, in twelve cases, *Neisseria meningitidis* in two, *Diplococcus pneumoniae* in one, and no organism could be isolated from the four remaining cultures. In the latter four cases the cerebrospinal fluid was frankly purulent.

Multiple serum and cerebrospinal fluid tetracycline levels, as well as appropriate cultures, were obtained, and therapy was instituted with intravenous tetracycline,* 75 mg. per kilogram per day with other necessary supportive measures. The details of administration adhered to the recommendations of the manufacturer. The dosage used was larger than recommended for lesser infections because of the serious nature of meningeal infections.[3, 22, 23] Intravenous administration was continued for seventy-two hours, although the intramuscular route was occasionally used after twenty-four hours. After the third or fourth day the drug was given orally in similar dosage, and the therapy was continued until complete recovery, indicated by normal temperature for seven consecutive days and

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*The trade name of Lederle Laboratories Division, American Cyanamid Co., for tetracycline is Achromycin. The medication used in this study was generously supplied through the courtesy of this company.

disappearance of spinal fluid abnormalities, occurred. Sera and cerebrospinal fluid specimens were assayed immediately or promptly stored at –5° C. for later laboratory analysis. The determinations were performed by the serial twofold tube dilution method utilizing *Bacillus cereus** as the test organism.[23, 24] Control specimens were assayed before freezing and at varying intervals from several to 60 days. No deterioration of tetracycline in the stored samples could be demonstrated. Stool cultures were obtained at intervals during therapy.

CLINICAL RESULTS

The over-all results for the nineteen patients were eighteen recoveries and one death. Among the eighteen who recovered, one patient required additional antibiotics and four suffered complications: two had subdural effusions and two developed micrococcal infections. Summaries of these cases follow so that the reader can evaluate the efficacy of tetracycline therapy. The single fatality occurred in a 2-month-old male infant with congenital hydrocephalus, who developed meningitis following a ventriculospinal shunt procedure. He had fever postoperatively for which intramuscular penicillin was empirically administered. The fever persisted and five days later meningeal signs appeared. Cerebrospinal fluid examination revealed 5,000 polymorphonuclear cells per cubic millimeter and the culture yielded *Micrococcus pyogenes* var. *aureus*. Tetracycline therapy as outlined above was started and penicillin discontinued. The patient responded favorably and the cerebrospinal fluid cleared. But progressive hydrocephalus due to the failure of the neurosurgical procedure caused death seven months later. A post-mortem examination showed congenital obstruction of the aqueduct of Sylvius without inflammatory disease.

*Graciously supplied by Lederle Laboratories Division, American Cyanamid Co.

THERAPEUTIC FAILURE WITH TETRACYCLINE THERAPY

The therapeutic failure occurred in an 8-year-old girl who was admitted with a stiff neck and back following the onset of acute fever and headache. Cerebrospinal fluid examination revealed 12,700 cells per cubic millimeter, chiefly polymorphonuclears. Cultures of the blood and spinal fluid yielded *H. influenzae*, type B. Intravenous tetracycline therapy was started, and by the fourth day she appeared alert and the cerebrospinal fluid cell count had been reduced to 1,135 cells, 75 per cent lymphocytes, but the culture showed beta enterococcus. Thrombophlebitis developed at the site of intravenous administration, and to counteract continued spinal fluid pleocytosis and growth, both sulfonamides and streptomycin were added to the therapy. On the seventh day, despite a spinal fluid cell count of 135, erythromycin was substituted for streptomycin and sulfonamides because disk sensitivity tests had revealed that the enterococcus was very sensitive to this drug. The fever persisted but skull and mastoid roentgenograms remained normal and subdural effusion was considered unlikely. Electroencephalogram was diffusely abnormal. The patient ate well, remained alert, and did not appear ill in spite of daily temperature fluctuations between 36° and 38° C. Medication was discontinued after twenty-three days and she was

discharged in good condition. On reviewing this case in retrospect we wonder if the beta enterococcus could have been a contaminant rather than a true secondary invader.

CASES COMPLICATED BY MICROCOCCUS PYOGENES INFECTION

The first patient was admitted with a history of fever and cough for which penicillin had been administered. Before entering the hospital she became stuporous, and on physical examination she appeared critically ill with fever, stiff neck, and shallow respirations. Initial cultures of blood, nasopharyngeal, and cerebrospinal fluid yielded *Diplococcus pneumoniae*. The cerebrospinal fluid revealed 1,000 cells per cubic millimeter, and on smear numerous gram-positive cocci were seen. Roentgenogram showed haziness in the left mastoid air cells. She was treated with tetracycline and supportive measures, and a left mastoidectomy was performed. Her condition improved rapidly but intermittent fever continued in spite of a clear cerebrospinal fluid. The mastoid wound drained purulent material from which *M. pyogenes* var. *aureus* was cultured, sensitive to penicillin. Accordingly penicillin was given, with remission of fever and healing of the mastoid area. The patient was discharged on the twenty-sixth hospital day.

The second patient had a mild respiratory infection for two days and developed fever, vomiting, and convulsions just before admission to the hospital. Physical examination revealed a stuporous boy with inflamed eardrums, a stiff neck, and positive Kernig and Brudzinski signs. Examination of the cerebrospinal fluid showed 4,200 cells, 99 per cent of them polymorphonuclears. *H. influenzae*, type B, was isolated from nasopharyngeal, blood, and cerebrospinal fluid cultures. Intravenous tetracycline therapy was started and changed to the intramuscular route four days later. A low-grade, intermittent fever continued in spite of rapid improvement of the cerebrospinal fluid. On the eighth hospital day an abscess was noted in the right buttock, at the site of intramuscular tetracycline injections (Fig. 1). Subsequently purulent material

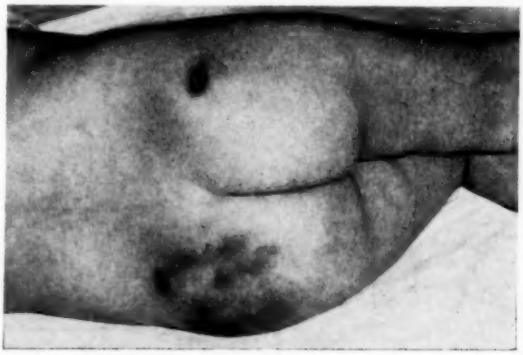

Fig. 1.—Tissue reaction and necrosis following repeated injection of tetracycline intramuscularly, 75 mg. per kilogram of body weight per day. Case 6.

drained from this abscess and cultures revealed *M. pyogenes* var. *aureus*, sensitive to erythromycin. This drug was given instead of tetracycline on the seventeenth hospital day, with prompt healing, and the patient was discharged twenty-seven days after his admission, completely recovered.

Subdural Effusions.—There were two patients who suffered subdural effusion in this series. Both had *H. influenzae*, type B, meningitis with prolonged fever being the cause for investigating the subdural space. The condition cleared completely in one of the patients, with repeated needle aspiration, and the other required craniotomy with removal of the subdural membrane. Both children were normal in appearance and in development six months after their acute illness.

TETRACYCLINE SERUM AND CEREBROSPINAL FLUID LEVELS IN ACUTE PURULENT MENINGITIS

Simultaneous serum and cerebrospinal fluid concentrations were measured twenty-four, forty-eight, and seventy-two hours after initiation of intravenous therapy, as well as at other varying periods, in the cases of meningitis described above. The dosage was 75 mg. per kilogram of body weight per day, and this was divided into four equal doses at six-hour intervals. Fig. 2 shows excellent tetracycline serum concentrations ranging from 3 to 24 μg per milliliter after twenty-four, forty-eight, and seventy-two hours of intravenous tetracycline therapy, but dropping on similar oral dosage from 3 to 0.38 μg per milliliter. Fig. 3 demonstrates excellent tetracycline concentrations in the cerebrospinal fluid within twenty-four hours. The range was 0.75 to 3 μg per milliliter. No accumulation of the drug in the cerebrospinal fluid occurred. Cerebrospinal fluid values obtained on similar oral dosage were considerably lower, ranging from 0.19 to 1.5 μg per milliliter of fluid.

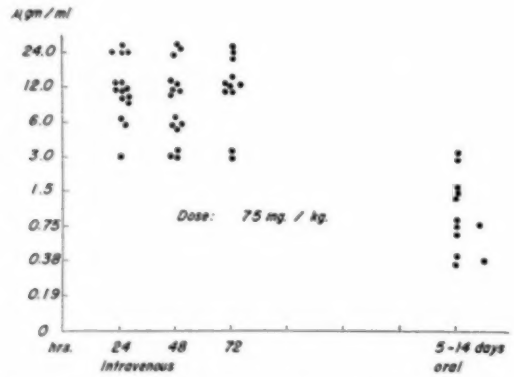

Fig. 2.—Serum levels at twenty-four-, forty-eight-, and seventy-two-hour intervals obtained while on tetracycline, 75 mg. per kilogram per day.

COMPLICATIONS DUE TO DRUG THERAPY

Mild gastrointestinal disturbances occurred in five patients. None required the discontinuance of medication. Local inflammatory changes at

the site of intravenous injections of tetracycline occurred regularly with the dosage used. Two patients developed areas of necrosis and sloughing due to the infiltration of the drug into surrounding subcutaneous tissues.

The intramuscular administration of tetracycline caused pain at the site of injection and three of the nineteen children developed abscesses of the buttocks. Low-grade fever was commonly noted with intramuscular therapy. One milligram of cortisone was added to each 100 mg. of intramuscular tetracycline in an effort to minimize local tissue reaction. Cortisone seemed to reduce both pain and local tissue reaction, but the results were not clear-cut.

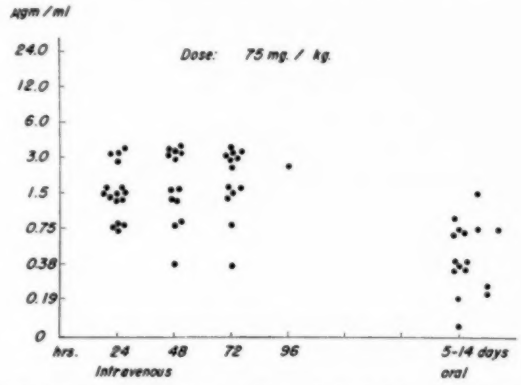

Fig. 3.—Cerebrospinal fluid levels at twenty-four-, forty-eight-, and seventy-two-hour intervals obtained while on tetracycline, 75 mg. per kilogram per day.

DISCUSSION

With the exception of Micrococci, most gram-positive organisms are sensitive to tetracycline in a concentration range of 0.312 to 1.56 µg per milliliter of serum. Gram-negative bacilli being slightly more resistant are sensitive to a concentration range of 0.39 to 3.21 µg per milliliter. Previous data[26] show that 18.75 mg. per kilogram of tetracycline intravenously or intramuscularly results in reliable therapeutic concentrations of 3 to 12 µg for six hours. It is apparent that tetracycline enters nonpurulent cerebrospinal fluid in substantial amounts.[26] In purulent meningitis, both oxytetracycline[27] and tetracycline enter the spinal fluid adequately, but in the absence of inflammation, only minimal amounts of oxytetracycline may be found in the cerebrospinal fluid.[27]

The clinical response in the nineteen patients treated initially with tetracycline was prompt. In all but three patients tetracycline was the only drug utilized. We have not observed resistance to tetracycline in the case of any Hemophilus, Neisseria, or Diplococcus organisms isolated. Increasing resistance to tetracycline has been found in Micrococcus isolates, suggesting it is not the drug of choice for infections caused by this organism. Figs. 4 and 5 illustrate the prompt clinical response to tetracycline therapy seen in influenzal and meningococcal meningitis.

Thrombophlebitis at the site of intravenous administration is a distressing feature with intravenous tetracycline in the dosage used by us. The

intramuscular form is too irritating to be recommended for routine use. Three deep abscesses occurred with subsequent prolongation of hospitalization. Oxytetracycline is better tolerated than tetracycline intramuscularly. It must be given deeply into the muscle tissue and the sites of injection must be constantly rotated. Recently Sakamoto[20] reported a case of anaphylaxis with recovery from a single intramuscular tetracycline injection. Chloramphenicol is used widely in the treatment of acute pyogenic meningitis and results are excellent. Although this series is small, it compares favorably with the cases in which the patients were treated with chloramphenicol[17, 21] and multiple antibiotic therapy.[15, 16] In addition aplastic anemia has not been reported with the use of tetracycline drugs, and for this

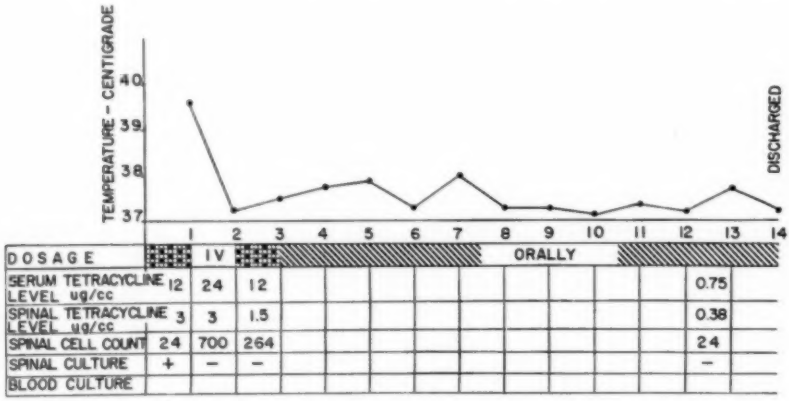

Fig. 4.—Clinical course of a patient with influenzal meningitis treated with tetracycline, 75 mg. per kilogram per day, correlated with serum and cerebrospinal fluid levels of the drug.

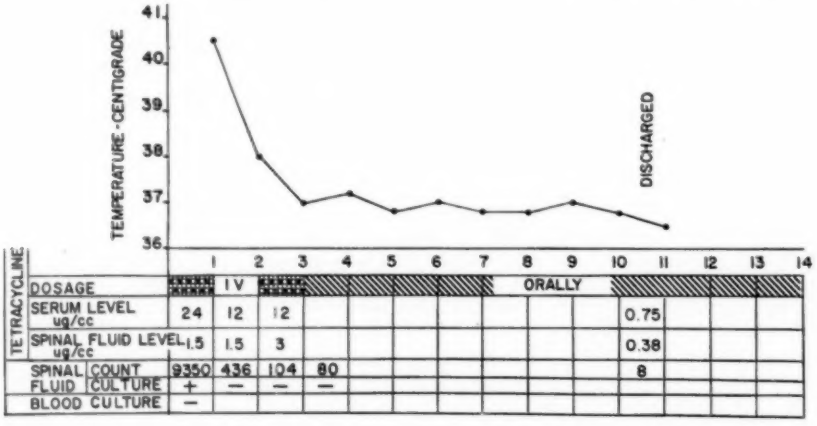

Fig. 5.—Clinical course of a patient with meningococcal meningitis treated with tetracycline, 75 mg. per kilogram per day, correlated with serum and cerebrospinal fluid levels of the drug.

reason they may be preferred to chloramphenicol. From our experience 50 to 75 mg. per kilogram of body weight per day provides adequate therapeutic serum levels of tetracycline for meningitis and larger doses seem unnecessary. Twenty to 30 mg. per kilogram, per day, of tetracycline is adequate for infections other than septicemia or meningitis. Two micrococcal infections occurred during the tetracycline therapy. The physician must be aware of the danger of superimposed infection with Micrococci and with gram-negative rods as well.[13] Enterocolitis[1, 45] and even septicemia[15] may occur as secondary phenomena when tetracycline or chloramphenicol[21] is used. Others[5, 25] have argued emergence of *Candida albicans* versus its presence as a normal inhabitant of the intestinal tract. In our cases twenty-three stool cultures taken after one week of tetracycline therapy revealed gram-negative rods in seventeen cultures and enterococci in six. Micrococcus was not cultured and *C. albicans* was isolated from only one patient. Our results are in agreement with those of Folz who found Proteus rather than Micrococcus[46, 47] as the primary organism in the stool, following tetracycline therapy. Six stool cultures revealed Pseudomonas, and we have observed septicemia in other cases due to this organism during both tetracycline and chloramphenicol therapy.

SUMMARY

Tetracycline alone was used to treat nineteen patients with purulent meningitis and was found effective in all but one patient. The use of the intramuscular form of tetracycline therapy is discussed and abscess formation described. Multiple determinations of serum and cerebrospinal fluid concentrations demonstrated that tetracycline readily crosses the blood-brain barrier in therapeutic concentrations in patients with acute purulent meningitis. The dosage of 75 mg. per kilogram of body weight, per day, of tetracycline given intravenously or intramuscularly produces effective therapeutic blood and cerebrospinal fluid levels. Parenteral administration produces three to six times greater concentration of tetracycline in the blood and cerebrospinal fluid than comparable oral dosage. The physician must remain alert and watch for superimposed infection with Micrococci and gram-negative organisms during both tetracycline and chloramphenicol therapy.

Technical assistance of Edythe G. Warwood is gratefully acknowledged.

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Emily Williams, born June 29, 1761. "An immature birth occasioned by drawing a tooth from her mother."

—WETHERSFIELD, CONNECTICUT, VITAL RECORDS.

BRAIN ABSCESS IN INFANTS

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THE accumulation of pus within the brain of infants has been commented upon infrequently in medical literature. That these reports appeared more frequently before the advent of antibiotics is understandable. Not more than two decades ago it was commonplace on the surgical wards to see individuals suffering from brain abscess, usually as a consequence of infection primarily in the ears and sinuses. With the marked decrease in the incidence and severity of these latter infections, the number of brain abscesses has accordingly diminished. Adequate treatment of a brain abscess with surgery and the use of appropriate antibiotics can usually be expected to result favorably. Since such intracranial infections are so seldom encountered in infancy it seems pertinent to call attention to the problem in order that early eradication of the infection may be carried out before irreparable damage is incurred to the developing brain.

Sanford,[1] in 1928, analyzed the findings in eighteen cases which he was able to accumulate from the literature. He added two of his own. As a preface to his discussion he comments that textbooks on pediatrics, surgery, and neurology, as well as general opinion, hold that brain abscess is indeed rare in infants. Of the cases studied he felt that roughly one third could be considered otitic in origin, whereas another third were of unknown etiology. Spina bifida and infection elsewhere probably accounted for the remainder of the abscesses. Further, he noted that although the general condition of 90 per cent of the infants when first seen was good, all infants exhibited convulsive manifestations at some time in their disease. Twenty-five per cent of the cases he reported had localizing neurologic signs, while 22 per cent of the cases exhibited some degree of enlargement of the head. The differential diagnoses seemed to lay between meningitis and tumor. All of these babies died.

In 1942 Braumoel and associates[2] were similarly struck by the paucity of reports on brain abscess in infancy, and could collect only twenty-six published cases from the literature. They added a case of their own. Sulfathiazole was available for treatment in this instance, but unfortunately the outcome again was fatal. By 1949, however, Farley[3] was able to present a preliminary report of an infant who developed a frontal brain abscess secondary to infection on the cheek. Using a combination

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of surgery and penicillin, a cure was effected. A follow-up report on this patient six years later noted that the child was then in school and was developing normally. Johnson and coworkers,[4] in 1953, commented upon three patients who had come into their hands, all of whom had died. Our purpose in this presentation is twofold; first, to describe three verified and one probable case of brain abscess, and, second, to recount our experience with the intraventricular use of Varidase.* Two of our patients died. By coincidence, all of the cases to be reported are premature male babies; three are one of twins.

CASE REPORTS

CASE 1.—Baby Boy T. was admitted to the hospital in August, 1953, at approximately 6 weeks of age, with the chief complaint of rapid enlargement of his head. He had had no fever or vomiting. Review of his newborn hospital record elsewhere revealed that he was the second born of twins, both of whom suffered moderately severe erythroblastosis. The mother was Rh negative, the infants Rh positive, and the Coombs tests were positive. Bilirubin levels were not determined. On the third day of life he had a temperature elevation to 102.8° F., which was of short duration, and began to have convulsive twitching. He was treated with penicillin and streptomycin, and later with Terramycin. A stormy convulsive course over the next week gradually subsided. No exchange transfusion was done, but he received multiple small transfusions of Rh-negative blood and was treated with ACTH. He was discharged at 36 days of age, having regained his birth weight of 5 pounds 4 ounces. No mention of any abnormality was made, and he was thought to be in good condition. No lumbar puncture was done. The head was not measured.

On admission the head appeared quite large and measured 16 inches. The temperature was normal. Subdural puncture was carried out in order to rule out the possibility of a blood accumulation within that space, and when nothing was found, the needle was directed toward the ventricle. Rather than ventricular fluid being obtained, a large abscess cavity was entered. *Pseudomonas aeruginosa* was the infecting organism. Aspiration of the purulent material and irrigation of the cavity with an aerosporin solution were carried out repeatedly, with the child being maintained on Terramycin by mouth as well as on blood transfusions. At length the returning fluid became clear and sterile. Because of the persistent enlargement of the head, craniotomy was carried out at the site of the abscess in order that the suspected fluid-filled cavity could be made to communicate with the ventricle. The relief obtained thereby was short lived, and additional shunting procedures were required, these likewise failing. The child died at approximately 7 months of age with hydrocephalus. Autopsy was not permitted.

CASE 2.—Baby Boy S., second-born twin, was delivered on Aug. 4, 1955, with a birth weight of 4 pounds. Health had apparently been normal except for a vague temperature elevation and poor appetite for two days when he was 3 weeks of age. He was noted to have an enlarging head when he was about 7 weeks of age, by comparison with his twin brother. The fontanel was also noted to be bulging at this time. At the age of 2 months he became extremely fretful, cried almost continuously, vomited persistently, and was admitted to the hospital. He was afebrile at the time of admission Oct. 10, 1955. Bilateral subdural tap was carried out in order to exclude the possibility of subdural hematoma. Instead, an accumulation

*Varidase (streptokinase-streptodornase), Lederle Laboratories.

of pus in the subdural space was found, and a similar thick, greenish, purulent material was identified when the lumbar tap was done. *Bacillus proteus* was isolated in pure culture from the material obtained. With a preoperative diagnosis of subdural empyema and meningitis, bilateral trephination at the coronal suture was carried out in an attempt to drain the subdural space. On the left side cortical herniation into the site of the trephine opening prompted the introduction of a needle into the subcortical area, where a large abscess was identified. *Bacillus proteus* was again isolated in pure culture from the purulent material of the abscess, and the child was started on Chloromycetin and streptomycin to which the organism had been found highly sensitive on in vitro studies. Daily aspiration of the purulent material accumulating in the abscess cavity was carried out, together with the instillation of 1 to 3 c.c. of a standard Varidase solution. It was our impression at this time that the brain abscess had likely ruptured into the ventricles, the infection progressively entering the subarachnoid space, for as the purulent material in the abscess cleared it was replaced by spinal fluid which was found similarly to be clearing on repeated lumbar taps. By the seventeenth day fluid from the left ventricular tap as well as the lumbar thecal space was clear and sterile. The fontanel remained full, and it seemed likely that the inflammatory process had interfered, at least in part, with the absorptive mechanism of spinal fluid. There followed several shunting operations, each temporarily successful and later failing, until March 20, 1956, when left ventriculomastoidostomy was carried out, and since which no further enlargement of the head has taken place. At each admission he was put on therapeutic dosage of Chloromycetin and streptomycin. It would seem at this writing that not too great damage to the developing brain had taken place, inasmuch as the patient, now at age 10 months, appears alert, grasps and chews on a rattle, vocalizes, pat-a-cakes, and appears almost equal to his normal twin in social development.

CASE 3.—Baby Boy H. was born approximately one month prematurely, on Jan. 1, 1956, the first of twins. Approximately three months earlier, the mother had premature rupture of the membranes for which she was hospitalized and received penicillin. The second twin died in the first few days of meningitis. In the first baby, rapid enlargement of the head took place in the third week of life; this was reported to be about two inches in one week. Lumbar and cisternal punctures yielded purulent spinal fluid from which a pure culture of gram-negative bacilli was obtained. He was treated with Chloromycetin, Aureomycin, and Mycostatin, with some improvement in that cells in the spinal fluid were reduced from 2,547 on Jan. 18, 1956, to 306 on Feb. 10, 1956, and sugar rose from 12 to 98 mg. per cent; however, the protein content remained very high (recorded as too high to read). The baby began to have convulsions and was referred to us on Feb. 14, 1956. At this time the spinal fluid was purulent with 9,550 white blood cells, mostly polymorphonuclears, and culture again showed a gram-negative bacillus, identified as *Aerobactor aerogenes* (Friedländer's bacillus) resistant to all antibiotics except Furadantin on in vitro studies. Furadantin was started orally at 5 mg. per kilogram per day. Daily aspiration of the accumulating ventricular fluid in increments of 40 to 60 c.c. was carried out, and 2 c.c. of a standard Varidase solution dissolved in 5 to 10 c.c. of saline solution was introduced into the ventricle. Within eighteen days the character of the ventricular fluid had changed from a thick, purulent fluid to a clear, normal-appearing fluid and culture at that time was sterile. Approximately one week after sterile fluid was forthcoming

from the ventricles, bubble ventriculography was carried out because of increasing enlargement of the head. Bilateral hydrocephalus was present, but the left lateral ventricle was seen to be disproportionately large as compared to the right. No displacement of the ventricular system was noted. It was felt that the left hemisphere, because of its greater destruction, could represent the site of an abscess, or at least cerebral empyema. Despite the fact that the intracranial infection had been controlled, the head continued to enlarge, the parents being unwilling to submit the child to shunting operations designed to control the hydrocephalus.

CASE 4.—Baby Boy J. was born prematurely on Dec. 3, 1955, with a birth weight of 4 pounds 8½ ounces. This baby was delivered spontaneously in cephalic position after normal labor, with prompt spontaneous respirations and cry. There were no apparent physical abnormalities. He did fairly well until December 7, when he began to regurgitate formula and large amounts of mucus. On December 9 he ran an elevation at 4 P.M. of 102° F. (rectally) and received 50,000 U. of penicillin intramuscularly. At 3 A.M. the following morning he still had an elevation of temperature, had a pasty color, and took formula very poorly with persistent regurgitation. At 6 A.M. the same morning he displayed a right-sided convulsion with generalized rigidity. He was first examined by us at 8 A.M. this same day. He was afebrile at this time and was quite spastic and hyperactive, convulsing with minor stimulation. The left pupil was larger than the right and dilated even more during the convulsions, which were generalized, although more prominent on the right side. There was constant bilateral horizontal nystagmus. The fontanel was flat and nuchal rigidity was present. The cry was shrill and piercing, the Moro response was hyperactive, and the sucking reflex was intact. A lumbar puncture was performed which was productive of yellowish-green fluid with the following findings: white blood count 7,450 per cubic millimeter, predominantly lymphocytes; protein 310 mg. per cent; sugar 68 mg. per cent. The baby was started on penicillin (aqueous) 300,000 U. every six hours intramuscularly, Chloromycetin 65 mg. every six hours orally, and streptomycin 25 mg. every six hours intramuscularly. His color remained cyanotic and waxy all day despite oxygen, and he continued to have episodic convulsive twitchings despite regular dosage of phenobarbital. The temperature ranged from 98° to 101.8° F. (rectally). At 7:30 A.M. on December 11 his condition appeared worse, with labored respirations, waxy complexion, and copious amounts of mucus. The fontanel was now tense and bulging and a bilateral subdural tap was performed, yielding about 4 c.c. of thick purulent material from the left side, none from the right side. A repeat lumbar puncture revealed purulent fluid which was not as thick as that from the subdural tap. At 10 A.M. he spiked an elevation of 104.2° F. (axillary) and suddenly ceased breathing at 10:55 A.M. Cultures from the subdural and spinal fluid grew out *Bacillus proteus*.

At autopsy a subdural collection of pus was found over the left frontal lobe in addition to generalized purulent meningitis. Section of the brain revealed most of the frontal lobe to be softened; this area of cerebritis surrounding a large, poorly demarcated and puss-filled abscess cavity.

DISCUSSION

A perusal of the above protocols would suggest that in none of our cases could a definite portal of entry for the infection be ascertained. Meningeal infection would seem the mechanism whereby infection secondarily invaded the brain in two of

these cases. Infection having gained access through the central nervous system, there would seem little propensity in these infants to wall off the disease—in contrast to what one usually encounters in the adult nervous system. This probably accounts also for the relatively large area of cerebritis and abscess, in some cases extending over one-half of a cerebral hemisphere. As will be seen in all of the cases cited above, the onset of the disease was apparent by the seventh week of life of the infant, and in two of the cases convulsions occurred as early as the fourth neonatal day. Only in Baby S. did convulsions fail to appear, and only in Baby J. was no enlargement of the head in evidence. The latter is, of course, accounted for by the fact that the child survived only eight days. *Bacillus proteus* was the infecting organism in two of our cases, while *Pseudomonas aeruginosa* and Friedländer's bacillus were each identified in another one of the cases. In each instance an appropriate antibiotic was available to which the organism was highly susceptible. To the best of our knowledge no extensive reports have as yet appeared on the use of Furadantin for the control of infections of the nervous system.

Since the abscess may rupture into or communicate with the ventricular system it seems imperative that the accumulating purulent material be removed as quickly as possible, in order to prevent it from blocking the subarachnoid absorptive mechanism. To this end Varidase was instilled into the ventricles in two of our cases. The concept of utilizing the streptococcal fibrinolytic substance, streptokinase, in treatment originated with Tillett and Gardner,[5] who first studied this extracellular enzyme and demonstrated its therapeutic usefulness. Later, Sherry and associates[6] isolated a second streptococcal enzyme, streptodornase, which digests the thick sediment of purulent exudates. In two of the cases reported above 1 to 3 c.c. of a standard Varidase solution was instilled into the ventricular system after withdrawal of up to 60 c.c. of purulent ventricular fluid, the procedure being repeated daily. Within eighteen days, in each instance, the ventricular fluid had returned to its normal water-clear appearance. No untoward reaction was apparent from the use of this material intraventricularly. Despite the fact that the infection was eradicated the resultant hydrocephalus proved an unsurmountable obstacle in one of our cases and continues to be a problem in another.

SUMMARY

Three proved and one probable case of brain abscess in infancy are presented. Two of the patients died. With use of the appropriate antibiotic in three cases, plus the intraventricular instillation of Varidase in two instances, the infections were brought under control. The problem of resulting hydrocephalus remains, however, and accounted for the death of one of our patients.

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Case Report

JOHN CHAPPEL, a healthy, sprightly boy, five years of age, on his return from school, at noon, on Friday the 24th of June, 1785, was seized with sickness at his stomach, and vomiting, which was soon after succeeded with thirst, heat, and restlessness. These symptoms continued through the afternoon and night, during which time he ejected every thing he took into his stomach, and in the course of the night and next morning, brought up ten large worms of the round kind. On Saturday morning I first visited him, at which time his pulse was extremely quick, small, and unequal; his countenance pale and sunk, his respiration quick and laborious, and he was so restless that it was with difficulty that his attendants kept him on the bed; his thirst was great, but he almost instantly threw up whatever was given to him. Nothing had passed his bowels since he was first taken ill, but his abdomen was not at all tumefied but rather contracted. He had his senses perfectly, but did not complain of pain in his bowels, or elsewhere . . . On Sunday morning we visited him again, but though the vomiting was not so frequent, his dejected countenance, difficulty of respiration, weak, quick, unequal pulse, and cold extremities, indicated his approaching dissolution. He died at eleven o'clock this morning. No evacuation was obtained from the bowels, during the course of the disease, by the many injections which were used, aided by the calomel, &c. On the afternoon of the same day, I obtained permission from the parents, to open the body, in company with Dr. Nesbitt and my brother. We found but one worm in the whole intestinal canal. The abdominal viscera were all found and well conditioned, except about two inches of the lower part of the duodenum, or upper part of the jejunum, which was inflamed and sphacelated, which appeared clearly to be the cause of his death. From the dissection it appears, that the disease was originally a true enteritis, or inflammation of the bowels, and it is highly probable that the worms were not at all concerned in the production of it; but being disturbed by the increased heat and disagreeableness of their situation, quitted it in search of a better.

FROM CASES AND OBSERVATIONS BY THE MEDICAL SOCIETY OF NEW HAVEN, 1788.

INFARCTION OF THE TESTICLE IN THE NEWBORN INFANT

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INFARCTION of the testicle with or without torsion of the spermatic cord has been considered to be rare in the newborn period. Twenty-four instances have been reported in the English literature since 1897. There are many more instances of this condition reported in the world literature which are not reviewed. The following two patients were treated in our hospital in a three-month period, though no previous cases are recorded in our pathological files.

CASE REPORTS

CASE 1.—Baby Z., a 3,575-gram, full-term infant was born April 24, 1956. The mother was gravida iii, Rh positive, and seronegative. The pregnancy was uneventful, and the six-hour labor and delivery were normal. The baby cried spontaneously. Physical examination in the delivery room was reported as normal by the obstetrician. Physical examination at 13 hours of age revealed a vigorous, normal, white male infant. The right spermatic cord was considerably thickened and firm. The testicle was enlarged to 2 cm. in diameter and was hard. The hemoglobin was 19 grams per cent and the white cells numbered 14,650, with a differential of 46 per cent polymorphonuclear cells, 50 per cent lymphocytes, and 4 monocytes. Roentgenogram of the chest revealed no abnormality. At 18 hours of age the testicle was still enlarged. There was no discoloration or apparent tenderness to pressure. At 44 hours of age, with no further symptoms, the right testicle was explored through a horizontal inguinal incision, using cyclopropane as anesthetic. The testicle was found to be enlarged and the lower portion of the cord was thickened. No definite evidence of torsion of the cord was seen. The testicle was indurated and purplish black in color. It was excised with the thickened part of the spermatic cord. The infant tolerated the procedure well. Recovery was uneventful except for a temporary drainage of seropurulent fluid from a portion of the wound for a few days. The infant was discharged, with the wound completely healed at 14 days of age.

The pathological examination showed the testicle measuring 1.8 by 2 by 1.4 cm. The parenchyma was light brown and finely granular. Microscopic sections showed almost complete obliteration of the normal architecture, with necrosis of the tubular structures. Remnants of spermatic tubules were seen but were surrounded and infiltrated by blood. Much of the tissue appeared pink and amorphous, but here and there disintegrating erythrocytes could be seen. Scattered round cells were observed in the latter tissue. Some regions contained fibrous tissue with many small vascular channels, forming a network and bearing brown pigment. No neoplastic tissue was seen. The tunica albuginea was thickened, fibrotic, and contained many lymphocytes and hemosiderin. The diagnosis was hemorrhagic infarction of the

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Fig. 1.

Fig. 2.

Fig. 1.—Hemorrhagic infarction of testicle. Almost complete obliteration of normal architecture with necrosis of tubular structures. Case 1.

Fig. 2.—Hemorrhagic infarct of right testicle with possible hematocele of cord. Small group of cells with indistinct outlines. Case 2.

right testicle. The changes were considered to be of a much longer duration than forty-four hours.

CASE 2.—Baby C. R. H., a white male, was born on June 10, 1956, to a normal, 23-year-old mother at full term following an uncomplicated first pregnancy, labor lasting 1¾ hours. He cried spontaneously. Shortly after birth it was noted that he had an imperforate anus except for a pinpoint perineal opening through which small amounts of dark green meconium passed. There was a left hydrocele. A more solid tumor which did not transilluminate was present in the right scrotal sac. He was transferred to Research and Educational Hospital at 24 hours of age. Here he appeared to be a well-developed white male newborn, weighing 8 pounds 11 ounces, with a good muscle tone and loud cry. The left testicle was difficult to define in the fluid-filled sac which transilluminated well. The right testicle was firm, nontender, and enlarged, and did not transilluminate well. Roentgenograms showed normal heart and lung outlines. The air-filled rectal ampulla was 2 or 3 cm. above the perineum. The hemoglobin was 17.5 grams and the white blood cells 9,000. The differential blood count showed 37 per cent polymorphonuclears, 61 per cent lymphocytes, and 2 per cent eosinophils.

At 41 hours of age the right testicle was explored and an infarcted testicle and spermatic cord were found. There was a rather firm, sclerotic band where the cord entered the testicle. Beyond this point the testicle was three to four times the normal size and greenish brown with the tunica albuminea adherent to the scrotal tissue. Though not unequivocably evident at operation, it was surmised some twisting of the cord could have occurred. The testicle and cord were excised.

Pathological description is as follows: an ovoid mass 3 by 1.5 by 1.6 cm. At one end there was a triangular-shaped piece of tissue measuring 2.5 cm. in its greatest diameter. The external surface of this mass was quite shiny, taut, and gray-tan. The center was dark and within the red-brown parenchyma was a dark red area measuring about 1.7 cm. in diameter. Multiple cross sections of the triangular tissue attached to the end of the mass revealed a light yellow tissue with a wide lumen which measured about 1.2 cm. The testicle bears an epididymis at one pole at the end where the triangular tissue was attached. Toward the opposite end the shell-like tunica was thickened to 0.4 cm. Its average thickness was 1.0 mm. Sections showed a few small groups of cells with quite indistinct outlines in one portion. An enormously dilated vein containing a slightly acidophilic and amorphous material was seen on one side. Smaller pieces of tissue showed markedly dilated blood vessels in a stroma of dense fibrous tissue. A moderate-sized duct lined by columnar epithelium was seen. Diagnosis was hemorrhagic infarct of the right testicle with possible hematocele of the cord with organization.

A transverse colostomy was done two weeks later and further perineal surgery will be done in the future.

DISCUSSION

Twenty-six cases, including these two, of infarct of the testicle in the newborn period are reported. Seven were designated idiopathic. Three were associated with strangulated inguinal hernia, and sixteen showed demonstrable torsion of the spermatic cord. Where torsion was present the etiology is not clear, but presumably cremasteric contraction is the force producing the twist. Such contraction could conceivably compromise the blood supply of the testicle without torsion of the cord. In instances of torsion there may be pain manifested by crying, but usually the babies are

asymptomatic. In all cases the scrotum is red or bluish and swollen. If the testicle is not in the scrotum but in the inguinal canal, the swelling is in the groin; if the affected testicle were undescended and intraabdominal, it might simulate surgical intestinal disease. The condition might not be suspected unless the increased size and hardness are palpated, and probably many cases have been missed in the past. Atrophic testicles found in older age groups may be the end result of such occurrences. Increased size and hardness should alert the examiner to the possible diagnosis. The most frequent condition simulating infarction is hydrocele. Here the usually soft consistency and translucence are quite different.

In the "idiopathic" cases some authors have considered torsion to be the etiological factor, but with spontaneous preoperative detorsion. This would explain the accompanying infarction of the contiguous part of the spermatic cord.

Torsion of the cord in early infancy has in the past been thought to be rare as compared to its incidence in older age groups. Recent reports may necessitate revision of this idea. Idiopathic infarction, though rare, is said to be even rarer at a later age than it is in the newborn infant. Unlike some reported cases, our patients did not have adherence of the testicle to the scrotal skin. There was no scrotal discoloration present in the first infant, though it was present in the second.

All such instances in infants should be explored as soon as possible to rule out neoplasm which, although rare, may be malignant even at this age, and to allow detorsion of a twisted cord whenever feasible. This offers the best chance for salvage of the testicle. Campbell[8] states that if the operation is done within the first four hours after onset, the testicle can be preserved. Usually the time of onset is uncertain and must be prenatal in cases diagnosed at birth. The general procedure has been to excise testicles with apparent total infarction. Longino and Martin[12] have not removed testicles in their patients, even though they appeared necrotic. They have not seen any difficulty in healing or seen suppuration in any, and they advocate leaving even a necrotic testicle in place for whatever endocrine function it may later contribute. Some advocate fixation of the opposite testicle as prophylaxis against a second torsion. Infarction of the second testicle, however, has never been reported.

SUMMARY

Two cases of infarction of the testicle in the newborn period are added to the twenty-four cases previously reported in the English literature. In both cases the testicle was excised and shown to have total hemorrhagic infarction of the testicle and contiguous cord.

Early recognition and immediate operation are necessary if the testicle is to be preserved.

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Pennsylvania and Heaven Too

The Christian Children born here are generally well-favored, and beautiful to behold; I never knew any come into the World with the least blemish on any part of its body, being in general, observed to be better natur'd, milder and more tender hearted than those born in England. . . Jealousie among men is here very rare, and Barreness among Women hardly to be heard of, nor are old Maids to be met with; for all commonly marry before they are Twenty years of age, and seldom any young Married Woman but hath a Child in her Belly, or one upon her Lap.

—GABRIEL THOMAS: HISTORICAL AND GEOGRAPHICAL ACCOUNT OF THE PROVINCE AND COUNTY OF PENSILVANIA, LONDON, 1698.

Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS 2½-year-old white female was brought to the hospital because of the development of ecchymosis and suspected meningitis. The patient had a history of chronic eczema beginning at 1 month of age. There had been frequent skin infections requiring incision and drainage on at least two occasions. One and a half weeks prior to admission, the patient again developed a secondary infection of eczema, with pustular lesions of the face. Four days prior to admission, she had the onset of pharyngitis with fine vesicular lesions along the edge of the palate. No therapy was given. On the day prior to admission the patient was slightly improved. On the day of entry she became drowsy, developed hemorrhagic areas about the facial lesions, and then petechiae on the flanks and legs. Nuchal rigidity was noted by the family physician, and the patient was admitted to the hospital.

The pregnancy resulting in this child had been complicated by maternal albuminuria, and the delivery by slowing of the fetal heart, dyspnea, and retraction in the first minutes of life. The patient's chest x-ray at that time revealed neonatal atelectasis, most marked on the right. The mother was allergic to cats. Otherwise the family history is noncontributory.

On admission the patient was well developed, well nourished, responsive, but restless and acutely ill. The temperature was 103° F., pulse 136 per minute, respirations 48 per minute, and the blood pressure 102/70 mm. Hg. The skin was slightly icteric, with dry, scaling eczematous lesions over the facial area which had superimposed, pustular, gangrenous, excoriated lesions 2 to 3 mm. in diameter. There were multiple petechiae and ecchymoses over the entire body. The right auditory canal was injected. A mild nasal discharge and injection of the pharyngeal mucosa without exudate were present. A few petechiae were seen on the right buccal mucosa. An enlarged 1 cm. lymph node was palpated in the right submandibular region. The lungs were clear, and the heart was normal. There was no hepatosplenomegaly. The neck was slightly stiff. Otherwise the neurological examination was negative. The remainder of the physical examination was within normal limits.

The patient was totally anuric, and no urine specimen could be obtained. The initial blood hemoglobin level was 9.3 mg. per cent, the erythrocytes numbered 4.07 million per cubic millimeter, the leukocytes 57,000 per cubic millimeter, and the platelets 16,000 per cubic millimeter. A bone marrow aspiration revealed a myeloid hyperplasia. The peripheral reticulocytes were 0.4 per cent of the total peripheral erythrocytes. The cerebrospinal fluid contained no cells, a normal sugar value, and a total protein of 15.6 mg. per cent. No bacterial growth was obtained on culture of this fluid. The initial blood chemistry values were recorded as nonprotein nitrogen 86 mg. per cent, pH 7.23, carbon dioxide combining power 8.4 vol. per cent, and sodium 110 and chlorides 80 meq. per liter. The serum bilirubin was 2.4 mg. at one minute, and 3.3 mg. per cent total. Blood cultures gave a growth of beta hemolytic streptococci and *Staphylococcus aureus*. Both organisms were sensitive to all antibiotics. A stool guaiac was positive.

The patient was given sulfisoxazole intravenously and aqueous penicillin 1,000,000 units intravenously every four hours. Blood levels of 30.7 mg. of sulfonamide decreasing to 10.8 mg. per cent were obtained.

The patient remained persistently febrile and totally anuric throughout the hospitalization. During the first night in the hospital, she had a generalized clonic convulsion and was subsequently noted to be completely unresponsive, with a moderate degree of cardiovascular collapse. She remained comatose and presented a picture of partial decerebrate rigidity. Paraldehyde sedation was used to control the seizures. On the second hospital day she continued to convulse intermittently and remained opisthotonic. She began to ooze blood from the mouth and vomited bloody material. The peripheral leukocyte count rose to 199,000 per cubic millimeter. Erythromycin and chloramphenicol intramuscularly were added to her therapy and the sulfisoxazole was discontinued in view of the anuria. The patient developed edema of the limbs and periorbital region. During the early part of the second hospital day, the patient was found to be extremely restless and then died quietly without any other event.

DISCUSSION

DR. ARNOLD S. RELMAN.*—This appears to have been a fulminating illness, beginning a week and a half before death, and characterized by septicemia, a thrombocytopenic purpura with a leukemoid reaction, and total renal shut-down. Whenever one is presented with the problem of total renal shut-down on the wards, one should think of two possibilities: first, postrenal obstruction and, second, circulatory collapse. The reason for this is that they are remediable and they are often overlooked, but here there was no reason to believe that there was any obstruction. There were no stones and no operation near the ureters, and there was no pain or colic of any sort. She was not in shock, and the blood pressure was normal. Terminally, after convulsions, she did go into circulatory collapse, but she was already anuric. Acute systemic infectious disease may

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rarely produce renal failure. I have never seen it produce such a fulminating picture. Fulminating hepatitis, the rapid form of a disease more common in adults than in children, usually gives rise to renal failure in adults who have some degree of preexisting vascular disease or obstruction.

What intrarenal processes can produce total renal failure? Necrotizing papillitis involving the tips of the medullary pyramids can produce an abrupt loss of renal function, but never a picture quite as fulminating as this, and I am inclined to consider it unlikely. Acute diffuse hemorrhagic glomerulonephritis can produce a fairly fulminating picture. We must stop for a minute to consider this diagnosis. Could this girl have had a septicemia following an infection of the skin with an alpha group A, B hemolytic streptococcus, and *Staphylococcus aureus,* which was followed by a diffuse hemorrhagic glomerulonephritis? One can see total anuria in acute, diffuse, hemorrhagic glomerulonephritis, but it usually does not occur so early in the course of the disease, and it usually follows several days of progressive oliguria with mahogany-colored urine, peripheral edema, and hypertension.

Why was the sodium so low? The serum sodium level of 110 meq. per liter is extraordinary. If one calculates the unmeasured anions from the sodium CO_2 and chloride values, one arrives at a level of approximately 12 meq. per liter. This is a normal value which is again unusual because the CO_2 content was 7 to 8 meq. per liter below a normal value. Since the accumulation of fixed acids is usually the cause of a depressed CO_2 level in uremia, the situation in this girl was unusual. There are, however, altered tubular states without uremia or increases in fixed acids where the CO_2 replaces the chloride ion. A possible explanation may be that the proteins were very low, in which case the unmeasured anion equivalents might have been reduced by 7 or 8 meq. per liter, and with the accumulation of fixed acids might have been raised to the resulting 11 or 12. We do not know whether she was vomiting, or whether she had much diarrhea before. Presumably she did not, but she apparently was not dehydrated. I suspect the low sodium is simply a reflection of a mortal disease that has destroyed the metabolic functions of the cells, so that they no longer can maintain normal electrolyte equilibrium. In adult medicine we certainly see very low serum sodium levels in patients who are not sodium depleted, but who are dying, or who are going to die of very severe generalized disease. It is just as if the cellular metabolic processes were beginning to die with the patient, and the sodium pump, or the potassium sieve, or whatever mechanism you want to describe for maintaining the composition of the internal and external environment begins to die at the same time. Such a low sodium value is not specific for glomerulonephritis. I think for that reason I am inclined to dismiss ordinary poststreptococcal or poststaphylococcal diffuse glomerulonephritis.

What other acute renal processes should we consider? The background of this girl, the mother's allergic background, the eczema, and the fact

that she had a skin disease, immediately call to mind the possibility of some sort of generalized hypersensitivity reaction. She had not received any therapy that we know of, and therefore we cannot definitely say this is due to the sulfonamide, or penicillin that she had received in advance, but I would be reluctant to rule it out merely because no history of drug ingestion was obtained. I think that the picture is entirely consistent with a generalized hypersensitivity reaction, including the thrombocytopenic purpura, as I understand it, with generalized vascular reactivity; one does get purpura, and the purpura may be nonthrombocytopenic, of the Henoch-Schönlein type. In other words, it may be entirely a vascular effect, or the purpurpura may be thrombocytopenic. I like the idea of the diffuse vascular disease, because that would explain the convulsions. Water intoxication and hyposmolarity, resulting from the renal shut-down and uremia, could explain the convulsions. Although jaundice occurs with septicemia, a diffuse vascular disorder also could explain her jaundice, and it could explain the fulminating course. When the kidneys shut down abruptly and totally, without obstruction or shock, one should suspect a vascular lesion in the kidney giving rise to severe ischemia. The vascular lesion may be gross, involving the renal arteries (as in thrombosis of the renal artery or a dissecting aneurysm), or it may be diffuse and involve intralobular vessels, the arcuate vessels, and the larger arterioles, or there may be a diffuse capillary prearteriolar and glomerular lesion. For that reason, I am inclined to think that the underlying disorder is some sort of hypersensitivity reaction, possibly of the periarteritis type or angiitis.

We must mention another disease, "thrombotic thrombocytopenic purpura." This was described in detail by Moschcowitz[1] in the middle 1920's, with multiple thrombi formed in arterioles and capillaries and rarely in venules throughout the body, the thrombi consisting of platelets with an endothelial reaction, the endothelium often growing up over the platelet thrombi. Sometimes there is actually organization and recanalization of these thrombi. This process is accompanied by a fever, an abrupt onset, marked and progressive hemolytic anemia, with mild leukocytosis, usually a shift to the left, sometimes a leukemoid response, and death occurring as a result of coma, purpura, bleeding, or of renal insufficiency. There are a number of reports in the literature of patients who have died of renal shut-down with multiple platelet thrombi, involving the small vessels of the renal cortex, fitting the description of diffuse vascular diseases with ischemic necrosis of the renal cortex. Most of the cases have a fairly severe anemia with marked evidence of hemolysis. She did not. The reticulocytes were normal, the bilirubin was of the direct reacting type, and I think that this is an argument against such a diagnosis, but there is much variation in clinical appearance of the disease.

I think we need to consider another diagnosis, that of septicemia with acute tubular necrosis, aggravated by the large dose of sulfonamide that was received. Septicemia or focal

bacterial nephritis rarely cause a catastrophe of this sort. Such lesions are focal in character, giving rise to a mild hematuria and albuminuria.

The clinician can be forgiven for being a little vague about these diagnoses, because pathologically, acute tubular necrosis blends off into cortical necrosis. There are many patients who die, let us say, with cortical necrosis of the kidney, due to multiple thrombi or arteriolar spasm, followed by multiple thrombi in the small, preglomerular vessels who, at post mortem, have some areas of cortical necrosis and other areas of classical tubular necrosis with the tubular rhexis described so beautifully by Jean Oliver.[2] Professor Sheehan[3] at Liverpool believes that confluent ischemic necrosis of the outer two-thirds of the cortex is simply an advanced stage of acute tubular necrosis, produced by more prolonged ischemia. From a clinical point of view, patients with severe cortical necrosis tend to be anuric, but those without ischemic necrosis of other structures than the tubules are likely to be only oliguric.

In summary, I am inclined to think that a pure glomerular lesion is unlikely, although I cannot rule it out. I believe we will find necrotic and probably occlusive lesions of small vessels proximal to the glomeruli; I suspect that we will find a diffuse disease, involving the kidneys, perhaps maximally but also other tissues; if it is thrombotic thrombocytopenic purpura, we should expect to find myocardial lesions, central nervous system lesions, pancreatic lesions, and other lesions. If it is a hypersensitivity type of angiitis, the adrenals and pancreas are notoriously involved, and we should find lesions there. The hematologic picture is a reflection, either of a platelet thrombosis phenomenon, or possibly simply a nonspecific reaction to septicemia with a secondary thrombocytopenic purpura and a leukemoid reaction. The role that the sulfonamides might have played in adding to the renal injury is speculative. We may find sulfonamide crystals or casts in the urine and in the tubules, but that still would not prove that it was due to sulfonamide. It could easily have been a superimposed factor here.

DR. FARBER.—Thank you very much, Dr. Relman. Dr. Janeway, would you like to continue the discussion?

DR. CHARLES A. JANEWAY.—The things that impress me as I read this over are the cataclysmic nature of the disease, its short course, and the system reaction as shown by the high leukocyte count. This child had contact with penicillin and sulfadiazine in the first three days of life and a long background of an allergic skin disease with probable recurrent infection. In order to produce a white count of this sort, I am not sure that the sepsis alone is enough, and, therefore, one almost has to assume that there is some massive inflammatory or necrotic lesion, and one certainly looks to the kidney as the most likely place for this to take place. I think that if one were to name this, one would say that it perhaps is thrombotic thrombocytopenic purpura, but by that we would simply give a name to something which may resemble other cases that have been described. We do not know the cause of this, but it blends into other kinds of reactions that involve the vessels. I would certainly expect that

we are going to find massive, diffuse cortical necrosis of the kidneys causing this total anuria. It may well be that the patient was previously sensitized with sulfonamides and that the reintroduction of sulfonamide at the turn of this acute illness delivered a "*coupe de grace*" and added a hypersensitivity element.

The other type of process that comes to mind every time we have seen one of these children with this syndrome is the generalized Shwartzman phenomenon. Here is a child who has a disease with infection and she seems to sort of drift along. Then all of a sudden hemorrhage starts to break out everywhere and within forty-eight hours the child is dead. Now this is the way the Shwartzman phenomenon behaves in the experimental animal, and whether this is going on here or not, I do not know. No one really knows what the Shwartzman phenomenon is, except that it is related to but is not the same as hypersensitivity. Some blood vessels have been altered by previous exposure to a toxin which can injure blood vessels by its direct action, but is this sensitization in the allergic sense or not? I do not think we know. When the generalized reaction occurs in the animal on an intravenous reinjection of a toxin for which the animal has been prepared, the animal, within a very short time, does have generalized diffuse cortical necrosis, and presumably must have renal shut-down. What this has to do with what happens in a patient like this, I do not know, but it seems to me that the analogy is very suggestive here. I think we had better wait and be instructed by the pathologist as to what really goes on.

DR. JOHN F. CRIGLER.—I would like to ask Dr. Relman what his explanation is for the electrolyte disturbance?

DR. RELMAN.—I do not understand it. I suspect that it is an example of the group of low sodium syndromes seen in terminal states, without loss of sodium and possibly not due entirely to water retention.

DR. JANEWAY.—Where does the sodium go in these patients?

DR. RELMAN.—That is a good question. I do not know. I imagine that it must go partly into the cells and partly into bone. You do not rid yourself of the problem by saying that it just shifts into cells. You have to say that it shifts into cells and that it becomes osmotically inactive. You have to lose osmotic activity.

DR. CRIGLER.—The other thing I would like to ask is, what would you have expected the potassium to be in this situation?

DR. RELMAN.—The high level of potassium may have its source in a number of factors including the anuria, the destruction of erythrocytes and tissue cells, the catabolic forces of a high fever, and, finally, the acidosis. In this type of situation, unless you can correct the electrolyte levels rapidly, the patient dies of potassium intoxication in a day or two.

DR. CRIGLER.—I am being a little monotonous today about this electrolyte picture, but it resembles closely that seen in adrenal insufficiency. I wonder if adrenal pathology was present?

DR. RELMAN.—A patient who has a renal insufficiency with a sodium down to 112 as a result of adrenal insufficiency would be severely dehydrated

and in severe shock. I do not believe the clinical picture of thrombotic thrombocytopenic purpura and anuria would be consistent with adrenal insufficiency. It is possible that, terminally, she had adrenal apoplexy, but something else was much more important. Something else was killing her, and maybe, just terminally, she had hemorrhages in the adrenals and elsewhere.

DR. CRAIG.—Dr. Winter saw this patient before her entrance into the hospital. He might like to say something.

DR. W. DAVID WINTER, JR.—This child did not receive chemotherapy in the few days immediately preceding her final hospitalization. She had a mild type of pharyngitis that was seen in the community. All of the patients improved without therapy. Discussion of the problem is particularly interesting, because the care of the patient when she came in was clearly directed toward the toxemia discussed in the past hour. It was only terminally apparent that while sepsis was a major problem, it was not the immediate cause of death. We discussed the use of cortisone during her hospitalization and, fortunately for the present discussion, it was not used.

DR. JACK METCOFF.—I wonder if, in addition to the lesions postulated by Dr. Relman, we do not have disseminated abscesses in a variety of tissues, including the kidneys?

DR. CRAIG.—This child, at autopsy, still had petechial hemorrhages, eczematoid dermatitis with crusted nodules, and a mild perivascular infiltration. No thrombi were encountered in the skin, and there were no particular alterations in the capillary endothelial cells. She also had a slight degree of icterus. The lungs were overweight, congested, edematous, and diffusely hemorrhagic. There was no really well-defined pneumonia present. The spleen had a few not particularly fresh reaction centers, containing hyaline material. In the liver we found a mild periportal infiltration, and, of course, with the tremendous white count throughout all the capillaries and sinusoids of the liver and other areas, there were an increased number of quite immature myeloid forms. The kidneys were overweight but not greatly so. They had numerous petechiae on their surface, but they were not particurarly striking. On section there was diffuse cortical necrosis (Fig. 1) with areas of complete necrosis and other areas of varying degrees of damage. The papillae and the medullary areas were comparatively spared. As Dr. Relman indicated, we found large numbers of fibrin thrombi within the glomerular capillaries, and afferent arterioles with necrosis of many glomeruli, and complete degeneration of many of the tubules. We found no evidence of an acute glomerulonephritis, abscess formation, or localization of this infection, with the exception of a small area about the submandibular glands described in the physical examination. Here there was a localized area of acute inflammation. We found no evidence of involvement of the small vessels, outside the kidney areas; therefore it is difficult to put this easily into the category of the Moschcowitz syndrome, where one has widespread involvement of the small

vessels. The bone marrow in this case was hyperplastic, and there were large numbers of megakaryocytes which seemed to be producing platelets in an adequate number, so that it was either a question of delivery from the bone marrow or an excess in utilization of platelets in the periphery which gave rise to the patient's thrombocytopenia. As Dr. Winter indicated, the septicemia was adequately controlled, and at autopsy neither of our cultures grew either of the organisms that were indicated. The brain was interesting, in that there were no specific lesions present. There was no evidence of involvement of any of the vessels.

We must agree with Dr. Relman that water intoxication was probably present since the brain was nearly 10 per cent overweight and was described grossly as being edematous. We have seen this picture in several other instances where fibrin thrombi have been limited to the kidney, so that I do not know whether or not we should consider this as a subdivision of the Moschcowitz syndrome. Most of the classical cases of Moschcowitz syndrome have lived considerably longer after the onset than did this child. What this clinical picture has to do with the generalized Shwartzman phenomenon, we still do not know, but in this case, more impressive than in some others, is the short duration of the disease. This is certainly analogous to the short time lapse between the sensitizing dose and the second dose that is used in experimental animals. The sensitization is apparently not related to the production of antibodies.

Fig. 1.—External and sectioned views of the kidneys, displaying petechiae and opaque areas of necrosis in the cortex.

DR. FARBER.—I remember well the excellent experimental work of Dr. Eugene Opie and Dr. Hans Zinsser, which we were given the opportunity to study. They produced the Shwartzman phenomenon by using pregnant rabbits and one dose of a colon bacillus toxin. This gave a beautiful bilateral, symmetrical, renal cortical necrosis, so that with a proper individual internal environment, one can produce, with a single dose, the same result as can

Fig. 2.

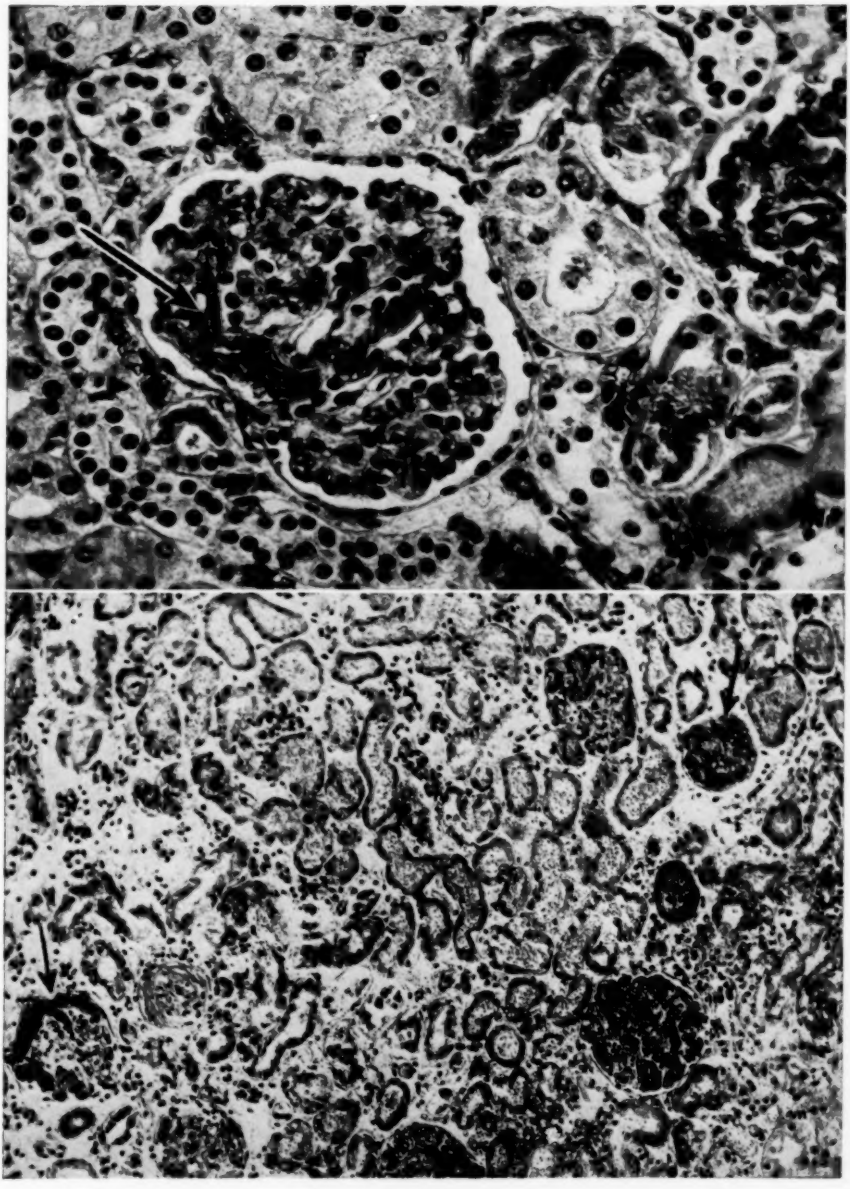

Fig. 3.

Fig. 2.—Kidney. At the arrow is an occluding fibrin thrombus in a capillary loop. The remainder of the glomerulus is normal. The surrounding tubules show only early degenerative changes. (Hematoxylin and eosin; ×400.)

Fig. 3.—Kidney. At the arrows are occluding fibrin thrombi in the glomerular capillaries. Other glomeruli show congestion and degeneration. There are advanced ischemic changes in the renal tubules in the center of the field. (Hematoxylin and eosin; ×180.)

be obtained with two separate consecutive agents. We will certainly assume that infection played a dominant role in bringing about the changes, both clinically and in the kidney lesion. I am impressed by the fact that much important experimental work in this whole cortical necrosis picture was carried out before World War II, and I am a little unhappy that an explanation has not yet been produced by a pathologist for this extraordinary picture in any precise terms. We have a clear diagnosis by Dr. Relman, but we are left with a considerable amount of doubt through our lack of understanding the exact chain of events that produced this picture. Second, of course, what Dr. Winters as the physician and all of us are very much interested in is how this chain of events could have been broken so that this end result would not have been reached.

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Medical Progress

CHANGES IN THE HEART AND LUNGS AT BIRTH

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THE first cries of a newborn baby, these are exciting sounds. Yet how incomplete is our understanding of the profound changes occurring during these moments. Most of our information has been obtained from animals, and in the last twenty years fine studies have greatly added to our knowledge. Probably no one has contributed more than Sir Joseph Barcroft.[1] His *Researches on Prenatal Life,* published in 1946, culminates a life of careful work and continues to be a source of stimulus and delight to all who read it.

Many species have been used to study prenatal and neonatal phenomena, and these have served to emphasize the variability to be found in nature. Barcroft[1] has wisely explained such variations not only on the basis of the different rates of growth in different species, but also on the degree of maturity at birth. While comparisons between animals and human beings are helpful and important, caution must be exercised in implying that a pattern of change or a reaction in one animal will be identical to that occurring in another species merely because the two animals may be the same age.

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THE FETAL CIRCULATION

The true function of the foramen ovale and the ductus arteriosus has not been appreciated until recently, even though these structures were described by Galen in the second century A.D.[2] Harvey,[3] in 1628, introduced the concept of a vigorous circular movement of the blood and integrated the best studies in earlier anatomical accounts of the fetal circulation. But, like others before him, he fell into the error of basing the theory of function on anatomical data, which, in some instances were inadequately supported by experimental evidence. The idea that blood could pass through the right atrium in two separate streams with little or no mixing was suggested independently by two workers, Sabatier[4] in Paris in 1774 and Wolff[5] in St. Petersburg in 1776. Despite experimental verification by Ziegenspeck[6] in 1905, this great contribution remained almost without effect on medical thinking, Kellogg[7] critically discarding it as recently as 1930. However, it was Kellogg[8] who realized the possibilities of blood gas analysis as a technique for the solution of certain fetal problems and who initiated the experiments in which the fetus was delivered by

cesarean section, the fetal and maternal circulation being retained and the fetal respiration prevented. These techniques were soon refined and perfected by Barcroft.[9] Finally in 1939 when Barclay, Franklin, and Prichard united their experience of cineradiography with Barcroft's experience, the first direct records of the circulation in the intact fetus were obtained.[10] These showed that in the lamb the arterialized blood in the umbilical vein passed rapidly through the liver, into the inferior vena cava (I.V.C.) via the ductus venosus, and from there into the left atrium, soon to appear in the aorta and the arteries to the head. When dye was injected into the abdominal I.V.C. or the superior vena cava (S.V.C.), it appeared to pass into the right atrium, right ventricle, and then into the descending aorta via the pulmonary artery and ductus arteriosus. Only a small portion of this blood appeared to circulate through the lungs at a slower rate. In a detailed study of individual films, the crista dividens appeared to separate the I.V.C. flow into two streams before the atria were reached, the stream from the ductus venosus being guided largely to the left atrium.

In the last five years Dawes and associates[11] have studied the fetal circulation in lambs by blood gas analysis rather than radiopaque dyes. While such a method of study has the disadvantage of assuming that confluent streams of blood have completely mixed at the sampling site, an assumption that is not always valid, it has the advantage of enabling a quantitative calculation of the blood flow distribution to be made.

Dawes' observations highlight two interesting points. The first concerns the separation of blood streams within the fetal heart at term. In the right heart blood mixes from the I.V.C. and the S.V.C. in the proportion of about 2:1, and in the left heart blood mixes from the I.V.C. and pulmonary veins in the proportion of about 4.5:1. The ultimate result is that the oxygen content of blood in the carotid artery is greater than that in the descending aorta (and umbilical artery), but the net gain to the fetus, as compared with the oxygen content if mixing had been complete, is small. The second point relates to the distribution of blood flow; 55 per cent of the combined ventricular output returns to the placenta, 10 per cent flows through the lungs, and the remaining 35 per cent flows through the fetal tissues.

The question is frequently asked whether the ductus venosus and foramen ovale have any physiological function apart from acting as by-pass channels. The foramen ovale has been shown to constrict with each beat of the heart.[10] However, there is still uncertainty about any such action by the ductus venosus. It has smooth muscle in its wall, and is innervated by the vagus. Reynolds[12] has recently suggested that it closes when the venous return from the placenta is high, diverting blood to the liver and preventing a sudden overloading of the heart. However, certain animals, including the horse,[1] do not possess a ductus venosus at full term, and Dawes[13] has shown that, when it is tied off in the fetal lamb, the pressure in both the umbilical vein and the I.V.C. does not change.

Recently an infant who died of massive aspiration, but who had shown no signs of fetal distress during labor, was found to have a fibrosed ductus venosus.[14] In all probability, in the light of Dawes' studies, this was merely an incidental finding, but until the exact function has been clarified doubt will remain. Barcroft[1] believed it perhaps less important that the ductus venosus should be patent during fetal life than that it should be closed during adult life, for, were it to open it would form an anastomosis between the portal and hepatic veins, a sort of Eck's fistula, by which blood coming from the alimentary canal could by-pass the liver and reach the general circulation without its contents being subjected to the beneficent chemical regulation of that organ.

THE FETAL LUNG

Opinions regarding an intrauterine function of the fetal lung are still conflicting. Methods of study have been dependent on morbid anatomy, the tissues being subjected to changes through post-mortem action or distortion by the various dehydrating processes necessary for fixation. The technique of studying microscopically unstained live lung tissue in newborn fetal mice, developed by Krahl,[15-17] has shed new light on this subject. Together with electron microscopy, these methods are giving a final answer to many of the arguments. Several anatomical points are not only interesting but also important both in regard to the fetal properties of the lung and the subsequent postnatal expansion properties. The cuboidal shape of the cells lining the fetal alveolus has been clearly shown,[18-20] giving the appearance of a gland, the cells almost entirely filling the lumen. The net of fine elastic fibers which intricately surrounds the alveolus, so well described by Miller,[21] deserves re-emphasis. Finally the presence of an unopened capillary network lying between the coiled arterial capillaries along the alveolar ducts has been demonstrated by Reynolds.[22] He states that tremendous resistance to passage of blood is produced by the convolution of these vessels and contributes to the small pulmonary blood volume and relatively slow circulation rate in the lungs.

FETAL RESPIRATORY MOVEMENTS

Fetal respiratory movements have been known to occur in human beings since 1888.[23] Interest was revived with the demonstration of such movements in fetal rabbits by Snyder and Rosenfeld[24] in 1937, and it was concluded that in all probability there was a tidal flow of amniotic fluid into the fetal lungs, the flow tending to condition the fetus for extrauterine respiration. When Davis and Potter[25] showed that radiopaque dye injected into the human amniotic cavity prior to cesarean section was present in the lungs after delivery, the story seemed complete. However, the dye was not revealed by x-ray in four out of the sixteen immature infants and was absent or questionably present in five out of the ten mature infants. At this time Windle and associates[26] again pointed out that fetal respiratory movements did not occur under physiological conditions, at least in the guinea pigs, and that the results obtained by Potter could have been caused by operative handling at the time of delivery.[27]

The most detailed study of respiratory movements in utero has been made by Barcroft[1] on fetal lambs. While such movements may be readily induced from the thirtieth day merely by light tapping, first as a single spasm and later as a rhythmical burst of such spasms, they become increasingly difficult to evoke between the fiftieth and sixtieth days—finally only appearing if the fetus is subjected to asphyxia. With continued asphyxia, caused by occluding the umbilical cord, the lamb will make rhythmical respiratory efforts, then single spasms, and these will finally cease. The response of the respiratory mechanism thus seems to vary according to the degree of asphyxia.

As the idea that a tidal flow of amniotic fluid may occur normally has become less tenable, evidence that the alveoli actually produce fluid during the latter stages of gestation has been accumulating. The possibility was first suggested by Whitehead and collaborators[28] in 1942 in commenting on cases with congenital occlusion of the bronchus or trachea where the alveoli were well expanded.[29] Later Jost and Policard[30] described the lungs of rabbits, decapitated in utero at the twentieth day, the pregnancy continuing to the twenty-eighth day. In those animals where the trachea had become occluded by scar tissue, the alveoli were distended with fluid, while in others where the trachea had remained patent, the lungs appeared quite collapsed, having lost the small amount of dilatation normally seen at term.

The production of fluid from either the pharynx or the lungs has been noted by Reynolds[31] during studies of nonbreathing lambs with their placental circulation intact. The rubber bag of saline over the animal's head required frequent emptying due to the accumulation of fluid. Dawes[11] has also remarked on this phenomenon during similar studies, but with the trachea cannulated with an occluded saline-filled cannula. After half an hour or so, when the outlet of the cannula was opened, some 30 ml. or more of fluid would emerge. Whether this fluid is actually secreted by the cuboidal cells lining the fetal alveolus or whether it is merely a filtrate resulting from the high pulmonary arterial pressure, is still to be proved. Preliminary work on lung tissue from a three-month human fetus implanted in the pouch of the hamster favors the secretory mechanism.[32] Within a week the alveoli, no longer having any connection with a bronchus or trachea, became dilated with fluid and the cuboidal cells flattened, giving the appearance of a mature lung rather than one from a three-month fetus. Thus it appears that fluid is produced by the lungs, further that respiratory movements only occur abnormally in the later period of gestation, being excited by certain stimuli, especially asphyxia. The gasps occurring normally in the earlier stages of gestation, according to Barcroft,[1] cannot suck anything into the lung for three reasons: (1) the lung is solid, (2) the trachea is closed, and (3) the chest wall is soft. Even if the trachea were open, the rapidity of the movements, 40 to 80 per minute,[23] would preclude any movement of fluid through such fine passages. However, the presence of meconium and squamous cells in the

lung periphery of infants who have died following chronic intrauterine anoxia indicates that aspiration does occur in the older fetus, if the necessary stimulus is applied.

Newborn rats, after submersion in water for forty minutes, during which time they made respiratory movements, recovered on removal and apparently developed into normal adult animals.[33] The aspiration of fluid which occurred at this time did not appear to have any deleterious action on the respiratory mechanism. Potter[34] has poured 130 c.c. of amniotic fluid into the lungs of a full-grown rabbit. After thirty-five minutes the combined weight of both lungs was only 30 grams, showing that the fluid had been completely absorbed. However, when the lungs of a newborn lamb were expanded with fluid, Reynolds[35] showed that this was not absorbed due to the fact that the pulmonary arterial pressure remained high, higher than the plasma osmotic pressure. In a similar series of studies Dawes and associates[36] have shown that expansion of the lamb's lung with saline caused an increase in pulmonary vascular resistance and a decrease in pulmonary blood flow. (This is the opposite effect to that seen with a gas.) On subsequent ventilation with air or oxygen there was a reduction in the pulmonary vascular resistance. Thus, although newborn rats in some way can survive aspiration of fluid, and fluid can be absorbed by the adult rabbit lung, it seems almost certain that the aspiration of fluid into the mature lamb's lung will interfere with the normal postnatal readjustment processes.

THE FIRST BREATH

Why should an infant who has been lying in a comparatively inert state in utero suddenly begin to scream lustily the moment he is born? Both Eastman[37] and Potter[34] believe that this is not the initiation but merely a continuation of respiratory movements which have been occurring before birth. While such movements may occur normally, if irregularly, during the early stages of development, it has been noted above that a strong stimulus, such as asphyxia, is necessary to elicit these movements in the term fetus.[1, 26] Snyder and Rosenfeld[38] observed that anoxia, rather than stimulating these movements, apparently acted as a depressant in rabbits. However, both Barcroft[1] and Windle[39] observed a marked increase in fetal respiratory movements of lambs and kittens when 10 and 8 per cent oxygen in nitrogen were respired by the mothers. The disparity between these results may be due to a species difference or to the fact that Snyder and Rosenfeld's rabbits were given 4 per cent oxygen and 5 per cent carbon dioxide in nitrogen. In his analysis of this problem Eastman[37] has pointed out that in high altitudes profound lack of oxygen regularly produces apnea in adults. However, the respiratory enzymes of a newborn infant differ considerably from those of the adult[40] and therefore any comparison with the adult must be made with caution. Eastman adds that infants who are born with extremely low blood oxygen are apneic, while those with a high blood oxygen breathe more readily. This is only partly in accord

with recent studies.[41] On several occasions infants delivered either vaginally or by cesarean section, who have cried lustily within seconds of birth, have had no measurable oxygen in the umbilical arterial blood and very little oxygen in blood drawn from the umbilical vein. Therefore other factors including a high carbon-dioxide tension and a low pH also appear to be necessary for the infant to remain apneic. This evidence is in agreement with Barcroft's[1] original opinion "that the anoxemic gasp is the earnest of life to the individual." He goes on to emphasize that oxygen want is associated with respiration of a rather different type; the breaths are often gasps and generally part of a more extensive muscular movement.

Graham and Wilson[42] have concluded that a considerable portion of the total stimulus to respiration is derived from oxygen lack, acting through the carotid and aortic chemoreceptors, and not from a direct effect upon the medullary centers. The activity of the carotid body and sinus has been studied in newborn and fetal animals by Cross and Malcolm.[43] They were able to record directly the action potentials from the proximally severed sinus nerve, the patterns of response being similar to those in adult animals.

In measuring the effects of hypoxia on respiration, Miller and associates[44, 45] have shown that infants less than 24 hours of age tend to respond by hypoventilating. They postulate that this is due to a relatively poor chemoreceptor response. This interpretation is at variance with the findings of Cross and Warner.[46] Miller's graphs indicate that when the infants are given room air to breathe following inhalation of 12 per cent oxygen in nitrogen, their respiratory rates, tidal and minute volumes continue to fall for one and sometimes two minutes. Such a response could indicate that a respiratory center, depressed from hypoxia, was responding only because of increased chemoreceptor activity during the breathing of the low oxygen mixture. When such activity diminished with the breathing of room air, the true depression of the medullary center was revealed. This interpretation gains further favor since the breathing of high oxygen mixtures causes an immediate temporary diminution of minute volume.[47]

The newborn infant who is well oxygenated has been shown to be extremely sensitive to changes in atmospheric carbon dioxide, both the rate and depth of respiration increasing.[48, 49] Miller[49] has also measured the respiration in newborn infants subject to mild hypoxia and 5 per cent carbon dioxide. Both the tidal and minute volumes increased. However, the reduced response to added carbon dioxide of the adult respiratory center depressed with anoxia is well known.[50, 51] It would be interesting to know the lowest level of arterial oxygen saturation at which the newborn infant's respiratory center can be stimulated by carbon dioxide.

External stimuli as an initiator of respiration cannot be lightly dismissed despite the fact that Ahlfeld delivered several women in warm saline baths and found that respiration began as usual. Barcroft[1] uses the gasp in a refractory rabbit's fetus when the ear is firmly pinched to

illustrate the response. He has suggested that the flood of sensory impulses from the skin, the muscles, and joints are of first importance and must be taken as having a profound effect on raising the general sensitivity of the central nervous system. However, no one has yet devised a way by which the role of such stimuli can be evaluated.

Whatever the final word on the factors controlling the first few breaths may be, we do know that within a few minutes of birth a normal infant, by his own respiratory efforts, becomes fully oxygenated[52] and he will continue to breathe with relative regularity. Until more evidence is available we must assume that the continued rhythmical activity is controlled in the same way as in the adult.

PHYSICAL CHANGES IN THE LUNGS WITH EXPANSION

Krahl's[53] motion pictures showing the first expansion of primary atelectasis at the periphery of the fetal mouse lung, viewed under a microscope, by the techniques previously mentioned, beautifully demonstrate the change which occurs on expansion. Atelectatic alveoli, appearing as rosettes of cuboidal epithelial cells in which there is no evidence of stretching, flattening, or separation, can readily be seen. When the lung is subjected gradually to negative pressure the epithelial cells first begin to flatten. Then suddenly the process rushes to completion with great rapidity, evidently when some critical resistance is overcome. The alveoli, alveolar sacs, and ducts now appear to be fully expanded. Once expanded, they never return to their original rosette formation, the epithelial cells continuing to remain flattened. If surface tension is responsible for the resistance, it is the surface tension of the cuboidal cell membrane and not that of two moist flattened surfaces lying in apposition. This latter state is found only in secondary atelectasis.[54] The anatomical change probably accounts largely for the difference observed in the expansion properties of primary and secondary atelectasis.[55] Expanded lungs which have become secondarily collapsed are more difficult to reinflate than lungs which have never been expanded.

ASSOCIATED CHANGES IN CIRCULATION WITH EXPANSION OF THE LUNGS

With the opening up of the alveolar ducts and alveoli there is a vast increase in the pulmonary capillary bed.[22] The lungs become capable of accepting the whole output of the right heart which has previously been shunted through the ductus arteriosus into the aorta.[2] Although neither Abel and Windle[56] nor Barcroft[1] were able to demonstrate an absolute increase in pulmonary blood volume after the onset of respiration, Everett and Simmons[57] have shown an average increase of 100 per cent by the sixteenth hour in a series of well-devised studies in guinea pigs, using radioactive iron.

Besides preparing the way for a greater blood volume, the expansion of the lungs, with the associated unfolding of coiled capillaries, has the effect of greatly lowering the pulmonary vascular resistance.[58] This is purely a property of lung expansion, occurring whether the lungs are expanded with air, oxygen, or pure

nitrogen.[59] Before ventilation is begun the pressure in the pulmonary arterial trunk is greater than that in the descending aorta.[58] It falls as soon as ventilation with a gas begins. In the lamb the low adult level is reached within three to five hours if ventilation is satisfactory. Recent measurements of the pulmonary arterial pressure in newborn infants[60, 61] show that the adjustment is subject to some variation, taking from three to fourteen days to fall to the adult level. Reynolds and co-workers[62] have further shown that not only does the pulmonary arterial pressure fall, but also that there is a more rapid circulation through the pulmonary vessels and an approximate fourfold increase in the volume of this blood flow.

Lind has dramatically studied this change by cineangiography, dye being injected seconds before the first breath. As soon as the lungs expand, blood appears to rush into them from all directions, pulmonary artery and aorta. The heart size is suddenly reduced and only gradually resumes its former size and shape as the blood distribution readjusts.

The systemic arterial pressure[58] also falls in the lamb as the lungs expand, but returns to its original level when the cord is tied. Although it has been predicted that a similar pattern of response would be found in the human being,[63] such has not been the case,[64, 65] the pressure remaining at about 80 mm. Hg before and after the onset of respiration and before and after the cord is tied. This may be due to the fall being too momentary to detect in human beings and the vessels in the cord constricting very soon after the baby is delivered.

CLOSURE OF THE FORAMEN OVALE AND DUCTUS ARTERIOSUS

The pressure in the right atrium is higher than in the left in the fetal state.[11] With the additional pulmonary blood flow concomitant with lung expansion, the quantity of blood entering the left atrium increased. This causes the pressure to rise above that in the right atrium and tends to hold the foramen ovale closed. The cessation of the placental circulation augments this pressure difference. The closure does not become sealed for several weeks, and should the right atrial pressure rise above that in the left atrium for any reason, a right-to-left shunt would be re-established.[66]

The venous angiograms of Barclay and associates[2] indicated that when the lungs were expanded, dye no longer flowed from the pulmonary artery to the aorta. From this it was inferred that the ductus arteriosus had functionally closed. The studies of Dawes and co-authors have proved these deductions incorrect.[11, 59] Using the method of blood oxygen analysis, they revealed that although the ductus lumen constricted as the arterial blood became more highly oxygenated, there was still a considerable flow through this vessel. The flow was not from the pulmonary artery to aorta as in the fetal state but in the reverse direction, and in some lambs it contributed as much as 60 per cent of the total pulmonary flow. A continuous murmur was found to have developed over the location of the ductus and could easily be heard shortly after birth. Such a change would not be revealed by venous angiography

because of the changed pressure relationship between the pulmonary artery and aorta. Similar flow changes have recently been shown to occur in the human being[60, 61] but as yet no continuous murmur has been reported. This evidence has revealed the continued patency of the ductus, even at 11 days in infants with apparently normal cardiovascular systems, although the vessel constricts in many cases by 72 hours. With increasing degrees of anoxia in lambs, the recirculation of blood through the lungs via this left-to-right shunt also increases.[11] However, profound anoxia with the associated rise in pulmonary arterial pressure appears to produce the opposite effect in human infants,[66, 67] the blood by-passing the lungs and flowing directly from the pulmonary artery into the aorta, as in the fetal state.

In a brilliant series of experiments, Dawes and associates[68] have further shown that the ductus is stimulated to constrict primarily by high oxygen levels. The constriction occurs in the presence of an elevated pulmonary arterial pressure and is unaffected by severing all connections with the central nervous system. Sympathetic amines will also cause the vessel to constrict in the presence of anoxia. This may have an important application in conditions of stress and anoxia in utero. Reynolds[22] has observed that in asphyxiated fetal lambs, the ductus begins to constrict within fifteen seconds, and the closure is complete within one minute. This causes cardiac engorgement and a marked increase in pulmonary arterial pressure.

MECHANICS OF LUNG EXPANSION

That intrapulmonary pressure as high as 35 cm. of H_2O was necessary to cause initial lung expansion was first suggested by Smith and Chisholm[69] in 1942. Ten years later Day and collaborators[70] demonstrated that secondary atelectasis in animal lungs could be corrected safely if a high pressure (40 cm. H_2O) was applied for a brief period of time. The use of –40 cm. H_2O pressures with perfect safety was reported by Donald and Lord[71] in their augmented respiration studies on infants, applying the negative pressure to the thorax. However, the idea has been accepted by both pediatricians and obstetricians with considerable caution. This reticence has in part been due to experimental results obtained from lungs of infants dying of nonrespiratory complications.[72] Pressures of 30 cm. H_2O were found necessary to effect expansion, but these pressures when applied for an indefinite period of time invariably ruptured the lungs. Postmortem autolysis could have also contributed to the rupturing. Reluctance to apply pressures greater than 30 cm. H_2O has also been due to false concepts derived from rubber balloons.[73] One must remember that the alveolus is surrounded by a fine net of organic elastic fibers which have an extraordinary tensile strength.[21] This allows a group of alveoli to expand—and to hold their expansion while another group expands. If the application of theories from experiments with rubber balloons were correct a small segment of atelectasis could never be re-expanded by positive pressure. Any pressure applied would

continue to expand the already expanded alveoli still further since, according to La Place's law, the pressure required to expand them would be less. However, the actual condition in vivo is quite different. During any case of open chest surgery, small or large areas of complete atelectasis frequently occur and can be readily expanded by the anesthesiologist.[74]

Dawes[59, 68] has measured the pressures which are necessary to adequately expand the lungs of newborn lambs, and has shown them to be in the region of 35 cm. H_2O. The studies of Day[70] emphasize that pressures even higher than this can be used with safety if the pressure is applied for a brief enough period of time. However, volume is also important. Dawes has shown that the lamb remains underventilated and anoxic, the ductus only partly constricts, and the pulmonary vascular resistance remains high if high pressures with an adequate tidal volume are not initially applied.

Karlberg and associates[75] have recently measured first breath in human infants. The pressure changes occurring in the esophagus with this breath were large, being 60 to 80 cm. H_2O. The volume of the first inspiration was also large, and in some instances was 80 ml. Much of this remarkable volume appeared to remain in the lungs as residual air, which would indicate that the lungs expand rapidly. Further studies of this type are indicated in order that we may establish the exact way in which lungs normally expand. We know that high pressure is necessary to achieve the expansion. The best way to apply these pressures has still to be determined.

On the basis of studies on stillborn lungs, a theory has been advanced that normal lung expansion is related to a high pulmonary arterial pressure.[76] However, when one considers that a high fetal pulmonary arterial pressure has no such effect in utero, and that it falls with lung expansion, such an idea becomes untenable. It is possible that a high pressure may assist in the initial unfolding of the new capillary bed briefly during the first few seconds of lung expansion, before the vascular resistance has fallen.

If the changes occurring at birth are to be appreciated, the state in utero must be fully understood. Until this time we cannot know which infants are dying because of failure to make the readjustment, nor can we hope to offer any rational therapy to those infants who may be unable to make the necessary readjustments themselves.

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Pediatric Profiles

Isaac Arthur Abt

(1867-1955)

DR. ISAAC ABT'S life was a remarkable example of great accomplishment and distinguished leadership in American pediatrics. He was outstanding as a clinician, teacher, scholar, author, and humanitarian. Dr. Abt was within less than a month of his eighty-eighth birthday when he died. His life covered a period of tremendous scientific progress in which he had himself been a leader for sixty years or more. A profile of Dr. Isaac Abt is in a sense a profile of pediatrics in America almost from its beginning to the present time.

He outlived those who could have given a first-hand picture of the early years of his career, but many of us knew him from his vigorous middle age on. He was already a famous pediatrician in his early forties when I was a medical student in Chicago. I just missed being one of his students because he resigned from Rush Medical College to become professor of pediatrics at Northwestern a year before I started my clinical work, but all of us knew him by reputation. Thirty-five years of practice in the same city did, however, give me the privilege of many associations with this great man. I became his friend and inevitably his admirer. This was the case with all of the pediatricians of my generation in the city, for his influence pervaded Chicago pediatrics to the very last years of his life. The scholarly attributes which characterized his whole professional life served to keep him abreast of medical progress and enabled him to participate actively and forcefully in pediatric activities as long as he was physically able to do so. My last intimate association with him was a striking illustration of his continued

participation. It was in 1946, and Dr. Abt was then 79 years old; he had been appointed by the Cook County Civil Service Commission to serve with me and two other pediatricians on a committee to conduct the examination of candidates for the pediatric attending staff of Cook County Hospital. These are formal written examinations held every six years. When we met to formulate the questions he appeared with a carefully written list. Dr. Abt's questions clearly showed not only his familiarity with the most recent developments in pediatric science and practice, but also reflected as well the wisdom gained from his long career as a teacher in the art of comprehensive evaluation of a student's knowledge. More of his questions were selected than of those of any other member of the committee. It was our function also to grade the papers; there were more than fifty of them. We held two evening sessions lasting until nearly midnight. It was tedious work but it had been fun working with Dr. Abt. He sat across the table from me puffing on a cigar, glancing up now and then with a twinkle in his eyes to make some humorous remark concerning the answer of a candidate. In grading, his judgments of each candidate were shrewd but always just. It was 11:30 P.M. when we finished our last grading session and went out for a midnight snack. All of us marveled at his energy, alertness, and wit. What thoughts might well have been going through his mind as he worked with us! These Civil Service Examinations had been inaugurated in 1898; he had himself taken that first examination almost 50 years ago. He might well have been thinking of the changes that had taken place in that half century. Changes in medical education and in the health and welfare of children, changes in which he had had an active part.

At the time of his birth, two years after the close of the Civil War, pediatries as a specialty was practically unknown. In Chicago, fifty miles from Wilmington, Illinois, where he was born, there were no pediatricians and only two in New York. Infant and child mortality was enormously high and the chances of a child reaching the age of 5 years were about 50 per cent. Bacteria as a cause of disease was just beginning to receive serious consideration in Europe and sanitation as a means of protecting the health of the public was practically nonexistent. In Chicago in 1875, when the Abt family moved to that city, health conditions were much the same as in Wilmington. A sister died of diphtheria at the age of 6 years, and a cousin of scarlet fever. These events made an impression on this 8- or 9-year-old boy. But his first real insight of medicine of that era came when at about the age of 13 he got an after-school and vacation job in a drugstore. This was not the drugstore of modern times but a true apothecary shop. Herbs and roots were ground by hand, infusions and tinctures were prepared there, and also compound cathartic pills, Seidlitz powders and citrate of magnesia. Young Abt helped in these apothecary activities, his interest in things medical was stimulated, and what he learned was helpful to him later. This experience was undoubtedly a factor in his decision to study medicine.

Isaac Abt and his twin brother were good students and had scholastic inclinations. In 1886, at the age of 19, they were sent to college, Isaac to Johns Hopkins and his brother to Yale. The Johns Hopkins University was then only ten years old but had already attracted wide attention in educational circles because of the distinguished scholars on its faculty. A hospital and a medical school were in the making; the hospital was being constructed and was put into partial operation that year but was not formally opened until 1889, and the medical school not until 1893. However, Abt got his premedical training under a group of eminent scientists, among them Ira Remsen in chemistry and W. H. Welch in pathology. William Osler came in 1889, and young Abt in his last year at Hopkins had the opportunity and privilege of ward rounds with him.

This was an era of new vistas in medicine. The germ theory of disease had only just been firmly established, Lister and Pasteur were still at work making their great contributions, Koch had announced his identification of the tubercle bacillus in 1882, and Klebs the diphtheria bacillus in 1883. Cellular reactions championed by Virchow and the fundamentals of immunity were under investigation. This was the atmosphere in which Abt was initiated into medicine and one can readily imagine its effect upon this scholarly young man.

When Abt had completed his premedical work in 1889, the medical school was not to be opened until 1893, so he had to decide where he should go to continue his studies. He sought advice from Dr. Welch who told him that none of the medical schools were very good but said, "It won't make much difference where you go, everything depends on you." Abt chose to go back to Chicago, where he entered the Chicago Medical College, the medical department of Northwestern University. The facilities there were meager and entrance requirements not strict. Few students had gone further than high school and some had no more than an elementary school education. Dr. Abt recalls that the school had three full-time paid employees: a janitor, a registrar, and a professor of chemistry. It was, however, superior to most other schools at that time in that it had a nine-month school year and a three-year course in contrast to the six-month school year and a two-year course of nearly all other schools. He found the members of the faculty to be excellent teachers. Some of the younger men, among them Frank Billings, had recently returned from a period of postgraduate study in Europe and were full of enthusiasm for the newer trends, especially in bacteriology and its implications. Abt was particularly stimulated by these men. The subject of bacteriology was not yet being formally taught in medical schools so Abt, together with three of his classmates, rigged up a laboratory of sorts in a closetlike room under the amphitheater and there began to study bacteriology on their own. This thirst for knowledge continued to be characteristic of Dr. Abt.

After graduation in 1891, he served as intern at Michael Reese Hospital, where he came to know some of the prominent physicians of Chicago of that period: L. L. McArthur, E. Willys Andrews, Christian Fenger, and others. Here also he began to

recognize the dearth of knowledge of children and their particular health needs. He saw in this field a gap in medical knowledge and decided that this should be his field. He read the writings of Jacobi, Henoch, Widerhofer, and others and his interest grew. There were but four or five outstanding pediatricians in this country then, so he decided to go to Europe to improve his knowledge. In Europe he studied under Widerhofer and others in Vienna and under Baginsky in Berlin and was in the midst of an atmosphere of investigation, particularly in bacteriology, pathology, and chemistry for which those centers were famous.

Back in Chicago in 1893, young Dr. Abt found the status of a specialist in diseases of infants and children was a lowly one; a "baby doctor," one who told mothers how to feed their babies, was the current concept. Establishing a private practice in pediatrics was an uphill job. But he was enthusiastic and ambitious, and wanted to teach. There was much to be done. Mortality and morbidity rates among infants and children were high. Diarrhea, diphtheria, scarlet fever, and tuberculosis were common killers and he was busy caring for sick patients in free dispensaries, hospitals, and gradually more and more in private practice. It was about this time that Von Behring produced diphtheria antitoxin. Dr. Abt was interested in its possibilities and in 1895 used it successfully on a desperately ill patient. This was said to be the first patient so treated in Chicago. Dr. Escherich of Vienna published a paper on pyuria caused by the colon bacillus which he had identified earlier. He called the disease colicystitis. This intrigued Dr. Abt and he looked carefully for patients having the symptoms described by Escherich, made the appropriate bacteriologic studies, and published a paper describing more than twenty cases. This was pioneer work in American pediatrics. It also greatly increased his consultation practice and that of many other pediatricians for a period of fifteen or twenty years, since few practicing physicians at that time had a microscope and fewer used one in the examination of urine.

Throughout his professional life he was a teacher. Professor of Diseases of Children at Northwestern Women's Medical School, 1897 to 1901; Associate Professor at Rush Medical College, 1902 to 1908; and Professor and Head of the Department of Pediatrics at Northwestern University School of Medicine, 1909 to 1942, was his academic record. He was a man of tireless energy. In spite of the ever-increasing demands of private patients and a growing number of requests for consultations he never neglected his teaching. His clinics and his lectures always showed careful and scholarly preparation. This was a distinguishing characteristic throughout his long career. It is said that his clinics were conducted in a uniform manner and with formal dignity. On the day preceding the clinic he selected two cases, one for shorter and one for longer and more exhaustive discussion. Once these had been selected there could be no substitutions. If his intern suggested that he present a new and unusual case admitted since the selections were made he would politely thank him for the suggestion and express great interest but firmly insist on the

original cases. He wished to carefully prepare for his clinical discussions. His rather formal dignity in his relations with students, interns, residents, and nurses and the implied expectation of respectful attention from them was a reflection of the manner of European professors. It was, however, in no sense an affectation; it was part of his inherent gentility. In his consultations he conducted himself with the same gentle dignity.

It was inevitable that with such industry, scholarly attainments, dignity, and clinical acumen he would receive recognition and be in demand as a consultant. His consultations took him not only throughout Chicago and the surrounding territory, but also to distant towns and cities in all parts of the Middle West. His professional reputation grew and it became tradition in the early years of this century that no child in the Chicago area with an obscure or serious illness had received expert care unless seen by Dr. Isaac Abt.

Pediatricians in those early years had their time so fully occupied with the care of sick children that they had little left for the well child. But Dr. Abt was aware of the need for and the possibilities of preventive medicine. He knew that something must be done and could be done to prevent some diseases through attack at their sources. He joined with others in 1908 in a crusade for pure milk to help prevent the scourge of infant diarrhea which was then taking such a heavy toll of lives. This crusade helped bring the dairy industry under legal control and led in 1911 to the establishment of the Infant Welfare Society of Chicago, of which he was for many years a member of its Board of Directors. In his autobiography *Baby Doctor* he tells of a meeting of the Chicago City Council before which representatives of the local dairy industry and representatives of the citizens organization campaigning for clean milk presented their respective arguments. Feelings were at high pitch on both sides and accusations were sharp and intemperate. Dr. Abt was a key speaker for the clean milk advocates and they won out. For those who knew Isaac Abt it is not difficult to understand why, nor to reconstruct the scene as this gentle, retiring but scholarly and dignified man convincingly presented his arguments. Here he demonstrated a striking quality which was manifested on many occasions during his life and came as a surprise to those who had not previously seen him in action. He was basically a gentle, quiet-spoken person, but when an issue on which he had firm convictions arose, his calm, unhurried, precise, and logical presentation had tremendous influence on his audience. They quickly recognized his intimate knowledge of the facts and his sincerity. It was quite disarming to his opponents.

It was this quality of forceful leadership plus his interest in child welfare, his prominence in the field of medical education, and his professional knowledge and ability which resulted in his election to many high offices in medical organizations. He was a member of the House of Delegates of the American Medical Association from 1919 to 1935, President of the American Pediatric Society in 1926, President of the American Academy of Pediatrics in 1930, President

of the American Association of Teachers of Diseases of Children, Chicago Medical Society, and Institute of Medicine of Chicago. He also held offices of importance in many other organizations. He was the recipient of many honors, among them Chevalier of the Legion of Honor of France, Honorary member of the German Pediatric Society, and the Distinguished Service Medal of the American Medical Association.

Morris Memorial Hospital for Children, a department of Michael Reese Hospital. It was to him that the Nelson Morris family proposed their original gift for this purpose. It was he who, after visiting children's hospitals in this country and in Europe and evaluating them, decided the type of construction and facilities which resulted in the best children's hospital in America at that time. And it

Isaac Abt signing copies of *Baby Doctor*, with his grandchildren in attendance.

By nature a modest person he did not wear his medals on his sleeve, but to say that he did not glory in the public recognition of his attainments would be false. He was proud of his accomplishments. He was also sensitive to rebuffs. I will cite one example. His was the leading role in building and developing the Sarah was his outstanding ability as a clinician and teacher that attracted an able staff and made it for nearly two decades a mecca for physicians seeking postgraduate pediatric instruction. But it was an integral part of a general hospital and subject to the over-all policies of the hospital administration. Some of these policies

and plans eventually conflicted seriously with what Dr. Abt felt was in the best interests of good pediatric care and pediatric teaching. As a result Dr. Abt resigned from the staff in 1925. This was a painful experience due in part to the failure of the administration to understand Dr. Abt's convictions regarding pediatric care and pediatric teaching and in part no doubt to his own obstinate pride. He was, I believe, never reconciled to this experience although he did eventually find a happy solution to his hospital and teaching problems at Children's Memorial Hospital in association with Joseph Brennemann.

Abt's Pediatrics, an eight-volume encyclopedia of pediatrics, published in 1923, was one of his greatest achievements. It is a monument to his enormous energy, scholarly character, broad knowledge of pediatrics, and personal friendship with eminent physicians in this country and abroad. Few, if any, American pediatricians have been as widely known and esteemed in other countries as he. Prominent European pediatricians were frequently guests in his home. On these occasions local physicians were often invited to meet them. Twice I had the honor of meeting Professor Heinrich Finkelstein of Berlin and once Professor Arthur Schlossmann of Düsseldorf at his home in this way. During the Nazi regime Finkelstein was forced to leave his position in Berlin. Dr. Abt then, after securing the cooperation of pediatricians in various centers in the United States, made possible an extensive lecture tour for him by which he was able to somewhat recoup his finances.

I have heard stories of how he would drive up to the homes of patients or to consultations in a chauffeur-driven, expensive car and charge enormous fees. These stories are, I am sure, quite untrue. He did conduct himself with formality and dignity but he was a tender-hearted man. In the early 1920's I asked him to see a patient with me. The family lived in a modest duplex apartment, in a somewhat blighted section of Chicago's West Side. It was a wholesome Irish family, the father a streetcar conductor; the home was scantily furnished, but well kept. He came directly from his office after a full day and was obviously tired. But he listened carefully to the story, made a thorough examination of the infant, and discussed the situation with me and patiently and understandingly explained the condition to the mother. Asked what his fee was he said twenty-five dollars. She went into another room and returned with the money which he took and put in his pocket. Then as we were putting on our coats at the door I saw him tuck the roll of bills she had given him into her apron pocket and give her a kindly pat on the back. She stood there, her eyes filled with grateful tears as we left. He did not know I had seen what he had done.

He was not one to make unkind remarks about a colleague. On a train going to a meeting of the Central States Pediatric Society in Memphis he sat with a group of pediatricians in the smoking compartment. It was one of those sessions when people not present were mercilessly torn to pieces. Dr. Abt stood up for each one of them. It got quite late and finally he said, "Well, I

shall have to go to bed and now you may say what you please about me."

The revolutionary movement of about 1850, which brought Bismarck into prominence in Germany, was also responsible for the migration to this country of many people of sturdy stock—clear-thinking, freedom-loving, and industrious people like Carl Schurz, Abraham Jacobi, and many others who became eminent citizens of our country. Dr. Abt's parents were among those who came from Germany at that time. His character reflected their influence during his early home life. In his autobiography he says of his father, "My father believed in the authoritarian organization of the family, and he was the authority. We children did not question his decisions—audibly at least—and we realized later that his rule, though firm, was also just. It would have been difficult for him to reconcile himself to the modern era, in which it is the child's word that is law, and to the progressive school where one pupil is reported to have asked, "Do I always have to do what I like in this damn place?" He loved his children and was proud of their accomplishments, but he regarded them, as all children, with skepticism. "So?" he would say, when Mother told him exultantly about the latest exploits of one of her clever babies, "So?" Then he would look thoughtful for a few minutes and add, "If babies are so bright, where do all of the grown-up simpletons come from?"

Thus an environment of honesty, justice, integrity, and industry bore fruit in the life of Dr. Abt. The characteristics we remember are his tireless energy, his broad knowledge of pediatrics, his ability as a teacher, his scholarly attainments, his humanitarianism, and, above all, his gentle, modest, and lovable personality.

Robert Frost, the poet, said, "Life begins with love and ends with wisdom." The sly twinkle in Dr. Abt's eyes and his knowing smile when he answered a question or discussed a subject were, I believe, a reflection of this wisdom.

In Dr. Abt we had a link with the past, a past so remote and strange as to be almost inconceivable and unreal. But he also lived with us in the present. And for this we can be thankful.

A. H. Parmelee

Comments on Current Literature

INTRAUTERINE FETAL OXYGENATION

THERE appears to be general agreement that interference with fetal oxygenation during intrauterine and early neonatal life remains a principal cause of fetal and neonatal death.[1] Yet, as has been emphasized by workers in this field, it is difficult in the human fetus to evaluate objectively the normal variations in prenatal physiology, and often difficult to recognize abnormal conditions which may be of importance in fetal and neonatal morbidity and mortality.

A remarkably direct approach to the problem is described in a recent article by Björn Westin[2] of Stockholm, "Technique and Estimation of Oxygenation of the Human Fetus in Utero by Means of Hystero-Photography," *Acta paediatrica*, March, 1957. Employing a specially adapted photographic instrument, colored photographs were obtained of the fetus in utero and of the umbilical cord and placenta. The hysteroscope was inserted into the uterine cervix, and by means of an ingenious puncture device and obturator, the slender instrument was carried through the fetal membranes, thus permitting direct examination of the fetus. "Vision was extremely good inside the fetal membranes and permitted detailed examination of the fetus, the placenta and the umbilical cord."[2] Colored photographic reproductions included in the publication are indicative of the remarkable clarity with which the author was able to visualize the fetal skin, various fetal parts, such as the foot, ear, and portions of the head, as well as the surface of the placenta and the umbilical cord.

Nine hysteroscopies were carried out by Westin on patients who were scheduled for therapeutic abortion. Length of gestation period in these nine patients was about fourteen to eighteen weeks. In only one instance minor bleeding occurred which ceased spontaneously within a short time. Westin found that bleeding could be avoided by finer technical adjustments. "Direct visualization of the umbilical vessels *in utero*" was possible, and "details of the placental surface and its circulation were clearly discernible." Observations made in the course of these studies indicate that the "oxygenation of the human fetus is high during the fourteenth to eighteenth weeks of gestation" and that the oxygen content of the cord vessels is lower after delivery of the fetus than it has been during intrauterine life. Further studies are in progress, and the author believes that the hysteroscopic technique, properly employed, offers new possibilities for obtaining information concerning the physiology of the fetus.

However, while such direct methods of study are informative, they are not practical for general use, and clinical evaluation of the fetus in utero, especially with reference to disturbances in fetal oxygenation, continues to be a difficult problem. For a number of years Edward M. Southern,[3, 4] now of the Mt. Sinai Hospital, New York, has been interested in this problem, pointing out that "the obstetric clinician is (still) forced to rely on changes in the rate and rhythm of the fetal heart sounds and the passage of meconium

in cephalic presentations for the diagnosis of intrauterine anoxia."[4] Since such observations are "subject to wide variations of personal interpretations," Southern recently undertook "to establish and determine possible prenatal electrocardiographic criteria for intrauterine anoxia"; this recent study is reported in the *American Journal of Obstetrics and Gynecology* for February, 1957. Improving on earlier techniques, such as those of Strassmann and Mussey,[5] and of Bell,[6] Southern utilized specially designed, more sensitive electrocardiographic equipment, which provides for "both oscilloscopic monitoring and continuous camera recording of fetal prenatal electrocardiographic complexes capable of analysis."[4] An attempt was made to correlate the fetal electrocardiographic variations obtained with those clinical conditions in which fetal intrauterine anoxia plays an important part.

Fetal electrocardiographic patterns were observed in forty-six normal cases during late pregnancy; these served as a control group, the electrocardiographic findings and oxygen saturation levels being used as a base line for the assessment of variations. The so-called "fetal distress series" included records obtained in twenty-two cases of clinically suspected fetal intrauterine distress, observations made upon patients in labor at term. Other groups studied included twelve cases of toxemia of pregnancy, eight cases of maternal hypertension, and eight cases of postmaturity. After careful comparison of the recordings in these groups with the fetal electrocardiographic tracings obtained for the normal fetus, Southern concluded that "alterations in the P wave, P-R interval, QRS voltage, S-T segment, and T waves are present in the prenatal fetal electrocardiogram in association with reduced oxygenation of the fetus."[4]

These changes were particularly striking in the group of twenty-two cases which had shown other signs of fetal distress, and the "earliest changes in the electrocardiographic pattern of the fetus in the presence of anoxia were in the S-T segments and T waves."[4] "In severe anoxia the changes consisted of depression of the S-T segment in Leads I and II. Prolongation of the S-T segment and isoelectric or inverted T waves occurred in a high proportion of cases."[4] These findings were well correlated with the reduced oxygen saturation of arterial cord blood observed at birth, and with the slow recovery from anoxia after delivery, as indicated by the lag in increase of oxygen saturation. For example, oxygen saturation in the "distressed infant" was 17.1 ± 4.1 per cent at two minutes (normal, 47.5 ± 5.1 per cent) and 40.5 ± 1.9 per cent at ten minutes (normal, 78.1 ± 2.1 per cent). Delay in onset of the cry in the anoxic group, which was seven minutes on the average, as compared with spontaneous "cry at birth" in the normal group, showed further correlation of the electrocardiographic findings with the clinical picture presented by the newborn infant. In three of the eight cases of postmaturity studied, fetal electrocardiographic tracings suggested intrauterine anoxia before the time of delivery. No definite correlation of findings was noted in the eclamptic and hypertensive group of patients.

In a discussion of fetal wastage resulting from anoxia in intrauterine life as compared to that in the immediate neonatal period, Southern refers to a Symposium organized by the Council for International Organizations of Medical Sciences (auspices of U.N.E.S.C.O. and W.H.O.), held October 1 to 15, 1951, and published in 1953 under the title, "Anoxia of the Newborn Infant."[1] Presentations and discussions at this symposium emphasized the importance of fetal oxygenation. In an estimation of the loss of infant life, 11,147 deliveries were classified from this point of view, and among the 11,147, intrauterine deaths

resulting from or associated with anoxia accounted for 92 cases, or eight per 1,000 births, as compared with 16 deaths, or 1.4 per 1,000 births, occurring from this cause immediately after birth.

Reliable objective evaluation of fetal anoxia in later intrauterine life will serve to alert the clinician as to possible therapeutic measures to be employed, and further studies of intrauterine physiology, wherever feasible, by such methods as hysterophotography and more exact electrocardiographic tracings should bring about better understanding and improved management of the problems associated with fetal life and the perinatal period.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

The problem of barbiturate poisoning has, quite appropriately, been the subject of considerable attention in the JOURNAL (Etteldorf and Woodbury, and J. K. Wilson in June, 1956; and Bizzarri and Giuffrida in March, 1957).

Dialysis with the artificial kidney appears to be the ideal treatment. This is the opinion of Elkinton and Danowski in the book *The Body Fluids*. They state that it is superior to intestinal and peritoneal dialysis. Berman (J. A. M. A. 161: 820, June 30, 1956) describes its effectiveness very dramatically.

This method is available at Georgetown University (Schreiner), at Bellevue Hospital in New York (Morales), at Peter Bent Brigham in Boston (Merrel and Guild), and at Cleveland Clinic (Kolff). There are others probably, and a list is being compiled. In addition to barbiturates, such poisons as salicylates, thiocyanates, paraldehyde, methanol, bromide, and doriden have been dialyzed out in human beings. Whenever a toxic dose has been taken or if the patient is in coma, dialysis should be carried out. Transportation should not be a problem these days. Even if artificial respiration has to be carried on during transportation, suitable apparatus is available.* Except for a brief mention by Etteldorf and Woodbury, the value of the artificial kidney has not been fully appreciated. It should receive first consideration in any seriously poisoned patient, both because of its effectiveness and safety.

JACOB GREENBLATT, M.D.

*Jefferson Ventilator manufactured by Air Shields, Inc., Hatboro, Pa.
Resuscitator manufactured by Stanton Scientific Co., Glendale, Calif.

News and Notes

Dr. Robert H. Alway, professor of pediatrics at the Stanford University Medical School, San Francisco, has been appointed acting dean of the medical school.

The *Institutes for Physicians and Nurses in the Care of Premature Infants* at the **New York Hospital-Cornell Medical Center,** under the sponsorship of the New York State Department of Health and the United States Children's Bureau, will begin their ninth year of operation in the fall of 1957. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers, and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration and that for nurses of four weeks' duration. Participants pay no tuition fee and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the 1957-1958 year are definitely scheduled to start on the following dates: Sept. 30, 1957, Nov. 18, 1957, Jan. 6, 1958. In addition, if the number of applicants is sufficient to warrant it, fourth and fifth Institutes will be scheduled beginning March 3, 1958, and

late in April or May, 1958. Early application for these Institutes is essential since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 East 68th St., New York 21, N. Y.

Two fellowships have been made available by the United States Public Health Service for training in *Pediatric Psychiatry* at the **State University of New York.** The program will be under the direction of Dr. Alfred M. Freedman. The fellowships are one year in duration and salary depends upon extent of training. These fellowships have been established to give a physician who has training in pediatrics one year's experience in the psychiatric aspects of pediatric practice. Fellows may begin their training on July 1, 1957, or thereafter. They must be citizens of the United States or have declared their intention to become citizens. Through clinical work and participation in seminars, the fellow will gain knowledge of the interrelationship of emotional and social factors and physical illness. The fellow will also have the opportunity to participate in the research program of the Pediatric Psychiatry unit, which currently is concerned with long-range developmental studies of prematurely born children, varying aspects of brain damage, and biologic aspects of mental illness. The fellow will also have an opportunity to be involved in other activities of the Department of Pediatrics. Communications in regard to these fellowships should be addressed to: Richard L. Day, M.D., State University of New York, College of Medicine at New York City, 450 Clarkson Ave., Brooklyn 3, N. Y.

A clinical fellowship in *Pediatric Cardiology* is offered in the Department of Pediatrics of the **Yale University School of Medicine.** This position is available from July 1, 1957, or any portion of the year so desired. The stipend is $4,500 per annum but the candidate must be a United States citizen and have had at least two years of pediatric training. Pediatric cardiac diagnostic and follow-up clinics, consultations, and assistance in the care of cardiac surgical patients offers considerable experience, together with the performance of various diagnostic examinations and assistance with research in the cardiovascular laboratory. The applicant should correspond with Dr. Milton J. E. Senn, Professor of Pediatrics, or Dr. Ruth Whittemore, Associate Clinical Professor of Pediatrics and Director of the New Haven Rheumatic Fever and Cardiac Program, Department of Pediatrics, Grace-New Haven Community Hospital, 333 Cedar St., New Haven 11, Conn.

The **New York Medical College—Flower and Fifth Avenue Hospitals** announces a postgraduate course in *Pediatric Allergy* under the direction of Bret Ratner, M.D., Nov. 6, 1957, to May 28, 1958, thirty sessions, Wednesdays, 9 A.M. to 4 P.M. The course consists of lecture-seminars, laboratory and clinical procedures, clinic work, and animal experimentation covering basic principles of diagnosis and treatment of allergy, and applied immunology in children. Applicants must be certified in pediatrics or have the requirements for certification. A limited number of allergists practicing with adults may also apply. Apply to Office of the Dean, New York Medical College, Fifth Avenue at 106th St., New York 29, N. Y.

Books

The Family Book of Child Care. Niles Newton, Ph.D., New York, 1957, Harper & Brothers, 479 pages. Price $4.95.

The author of this new book on child care for lay consumption is well known for her studies on breast feeding and maternal emotions. She is at present an assistant professor of psychiatry at the medical school of the University of Mississippi. Three physicians are listed as collaborators: Paul György, pediatrics; Irwin Marcus, psychiatry; and Thaddeus Montgomery, obstetrics. Obviously the text on these phases of child care was not written by the collaborators, but the addition of their names gives a semblance of medical authority. We doubt if they are in any way responsible for the general scope and contents of the book.

As a whole it is a remarkable mélange of what is more the author's opinions on a great many subjects than advice for parents on child care. The subjects range from diapering the infant to choosing a home, from silhouettes of the pregnant woman and drawings of the infant in utero to the choice of a church. The reviewer was almost fascinated by wondering what subject would turn up on the next page.

At times the statements are startling and sometimes quite amusing. For example, the following statement under a discussion of circumcision on page 77:

"If you decide to have your baby circumcised, plan to have circumcision done as soon as possible after birth, since it may be a frightening experience to an older baby or child. *If your boy is more than six months old, it's better to consult a psychiatrist before you have the operation done.*" (Italics ours.)

In a chapter entitled "How to Eat Well and Save Money" (a most intriguing title) we find on page 241 the statement: "Of course, by far the best way of saving money and getting wonderfully fresh fruits and vegetables is to grow them yourself." While backyard gardening may be an interesting hobby, it can be an expensive one, and is distinctly seasonal. The fruits and vegetables available in modern American markets today are usually not only better than home grown, but also cheaper in the long run, to say nothing of the variety available.

The author at times ventures an opinion in the field of economics (we looked for an investment list to provide for the child's future but for some reason this was omitted). While in general agreement with the soundness of the statement on page 288, *"Pay cash whenever possible"* (author's italics), her illustration of the point is debatable. She tells of how the Greens put $16.67 per month into a savings account and at the end of the year had the money to pay for a $200 television set. The Osborns bought the same set on time payments, and with carrying charges the set had cost $219 at the end of the year. While the Greens saved, as the author stresses, $19, the point is quite overlooked that the Osborns had the use of their set for a year for $19, while the Green family, we infer, had to content themselves with their radio.

The book is a most curious collection of material as these few quotes illustrate. Part is directly concerned with the subject, and part only by "remote control." There are better books on child care available for the laity.

When Children Ask. Margueritte Harmon Bro, Harper & Brothers, New York, 1956. 242 pages.

This is a refreshing book. In contrast to the psychodynamic dogma of most recent books on child guidance, here is one based upon the old-fashioned virtues of morality and faith, dignity of the individual and common sense.

Actually this book was first published in 1940. The present edition, rewritten by the author "sixteen years and thirteen grandchildren" later, has the feeling of richness of experience and deep understanding. This experience and understanding is brought to bear on fundamental questions of life and death; of God, of Jesus, of death, of prayer, of the Bible and of the church. This book, then, deals for the most part with religious questions. Yet, as Mrs. Bro states, the child's religious questions are not exclusively religious, for the domain of religion is concern with "first causes and final ends, with time values, with personality relationships. These concerns reduced to simplicities are also the domain of the child finding his place in the universe. In his mind (the child) is just asking about life."

It is questions about life thus defined that Mrs. Bro attempts to answer. Many of the questions asked do not have a final answer and to these no final or dogmatic answer is given. Instead, in a series of conversational vignettes, parable-like in themselves, various points of view are sketched. Throughout, the warm, human kindness of the author and her real depth of psychological insight are apparent.

This book can be recommended to the intelligent parent.

A. A. S.

The Doctor as a Witness. John Evarts Tracy, Philadelphia, 1957, W. B. Saunders Co., 221 pages.

Although pediatricians are rarely involved in legal proceedings, every physician must have at least a fundamental knowledge of medical jurisprudence. Legal proceedings involving the physician as a witness, either as to facts or as an "expert," have been increasing due to the steady rise in accidents and to an increase of suits brought for malpractice. In this monograph an emeritus professor of law at the University of Michigan has written a very readable and interesting book on the physician as a witness. It discusses his rights and obligations as a witness and goes into details as to his conduct under direct and cross examination by the lawyers. Certain special subjects, such as insanity from a legal standpoint, testimony in malpractice suits, and workman's compensation proceedings, are given individual chapters. Much sound and profitable advice to the doctor who finds himself on the witness stand will be found in a chapter entitled "What Makes a Good Medical Witness." Professor Tracy has avoided the usual technical legal presentation of the subject which makes most textbooks on medical jurisprudence dull and tiresome reading and more suited for the lawyer than the doctor. Rather, he has been most successful in writing a straightforward, readable discussion of the law and the doctor in the courtroom, which physicians will find not only informative, but also interesting reading. Highly recommended for the physician's library.

The Compleat Pediatrician, ed. 7. Wilburt C. Davison, M.D., and Jeana Davison Levinthal, M.D., Durham, N. C., 1957, Duke University Press. Price $4.25.

The simple fact that *The Compleat Pediatrician* has gone through six previous revisions since its first appearance and sold over 45,000 copies is sufficient testimony of the value in which it is held by the practitioner. The reasons for a new edition—the last was in 1949—are well stated by the author: (1) an enormous amount of additional pediatric information has accumulated during the past eight years; and (2) many of the "pediatric facts" collected in this book since 1919 are not disproved so reams of obsolete material have been deleted.

It is not necessary today to detail the scope, use, and place of *The Compleat Pediatrician.* It is not a textbook but a collection of thousands of pediatric facts arranged for ready reference. Dr. Davison has been joined by his daughter, Dr. Levinthal, also a pediatrician, in the preparation of the seventh edition. We can only repeat from a previous review in the JOURNAL, "A veritable mine of information."

Dorland's Illustrated Medical Dictionary, ed. 23. Philadelphia, 1957, W. B. Saunders Co., 1,598 pages. Price $12.50.

A book first published in 1950, which over the years has gone through twenty-three revisions, needs no discussion of its

value. The last revision was in 1951, and Dr. Dorland died in 1956. The new edition has an Editorial Board consisting of Drs. Leslie B. Arey, William Burrows, J. P. Greenhill, and Richard Hewitt. In the last six years many new words and terms have been introduced in medicine, and probably more in the last decade than in any similar previous period. Included in this edition is a table of Modern Drugs and Dosage compiled by Dr. Austin Smith. In order to hold the volume down in size, certain changes have been made, such as eliminating the detailed description of specific techniques. In the biographical field only the names of Nobel prize winners have been added. An excellent type font makes the dictionary easy to use.

Atlas of Clinical Endocrinology. H. Lisser, M.D., and Roberto F. Escamillo, M.D., St. Louis, 1957, The C. V. Mosby Co., 476 pages (148 plates, 3 in color). Price $18.75.

A beautifully illustrated atlas by two well-known endocrinologists from the department of medicine of the University of California Medical School in San Francisco. While the authors have not attempted a textbook on endocrinology, a brief summary of each of the sixty-three different endocrine disorders is included. The 148 plates are made up of from four to fifteen illustrations. The material is almost entirely from the records of patients studied at their clinic in San Francisco. The photographs are unusually good and the reproductions clear. As so many of the endocrine disorders make their appearance in infancy and childhood, the subject is one of great interest to the pediatrician. The atlas should be of help to the practitioner in reaching a correct diagnosis and instituting treatment.

Diabetes Mellitus. With Emphasis on Children and Young Adults. T. S. Danowski, M.D., Baltimore, 1957, Williams & Wilkins Co., 510 pages. Price $13.50.

An up-to-date text on the general subject of diabetes mellitus, with emphasis on children and young adults. Part one concerns biochemical and hormonal aspects; part two, manifestations, diagnosis, and therapy; and part three, developmental aspects and complications. The book should be of considerable value to the teacher and medical student because of the systematic way in which material is presented. The many references should make it valuable also to one conducting research in the field.

A. F. H.

Ageing in Transient Tissues. Ciba Foundation Colloquia on Ageing, vol. 2. Edited by G. E. W. Wolstenholme and Elaine C. P. Millar, Boston, 1956, Little, Brown and Co., 263 pages. Price, $6.75.

This volume includes the papers presented at the second Colloquia on Ageing under the auspicies of the Ciba Foundation, July, 1955. The first was held in 1954. The theme of the second symposium was the ageing of tissues whose normal life was shorter than that of the organism as a whole. The papers in the report with the discussions largely involve changes in ovarian and placental tissues and human red blood cells. E. C. Amoroso of the Royal Veterinary College of London presided.

Stuttering, ed. 2. Eugene F. Hahn, Stanford, Calif., 1956, Stanford University Press, 180 pages. Price $4.00.

The first edition in 1943 went through three printings, the last in 1950. Dr. Hahn died in 1944, and the second edition has been prepared by Elsie S. Hahn. The text presents the various theories or opinions on the causes of stuttering as held by twenty-three different authorities. It is a technical book for workers in the field rather than a text for the stutterer.

Editor's Column

COLD INJURY IN THE NEWBORN INFANT

IN A recent issue of the *Lancet* Mann and Elliott call attention to a highly fatal syndrome in young infants due to cold injury. Of fourteen babies with this clinical picture observed at Brighton during the past three years, eight died. The author estimates that the yearly number of deaths from this cause may exceed 100 in England and Wales.

Full-term as well as prematurely born infants are affected. The onset is in the first week or two of life, sometimes later, with apathy and indifference toward food. The cry becomes feeble. The body feels cold and corpselike and swelling of the extremities or other parts, such as the eyelids, may appear. Occasionally there is bloody vomiting or passage of blood by rectum. The urine decreases in volume and may cease entirely.

A constant feature is the reduction in body temperature usually well below 90° F. Nevertheless the facial expression is serene and does not suggest ill health. The face, hands, and feet are strikingly red, particularly the eyebrows, cheeks, nose tips, and chin. By contrast, some of the babies are pale, but despite this they do not look ill. Edema of the extremities is usual. Some of the edematous areas, especially in the legs, are firm to the touch (scleredema). This indicates a poor prognosis.

The blood sugar is reduced, in some cases to extremely low levels. The hematocrit is normal, at times elevated. Infections, chiefly rhinitis and ophthalmia and occasionally pneumonia and otitis media, complicate the picture. Convulsions, perhaps related to the hypoglycemia, may occur.

The duration of the illness is short—from a few hours to four or five days. The babies who go on to a fatal outcome begin to look ill. Pallor and cyanosis develop and finally respiratory failure. The most frequent postmortem finding is massive pulmonary hemorrhage.

Treatment is by gradual warming, intravenous or intragastric feeding with 15 to 20 per cent glucose solutions, and antimicrobial therapy to reduce the threat of infection.

Cases similar to those described in England by Mann and Elliott have been observed in Germany, Holland, and Palestine.

Scleredema and hypopyrexia are occasionally encountered in young infants in the United States. It may be well to consider the possibility of a causal relationship to exposure to cold.

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PYLORIC STENOSIS AND THE COMMUNITY HOSPITAL

ONE of the important trends in medical care has been the increase in the number of community hospitals coincident with the development of the huge medical centers in our larger cities. While the small community hospitals as a rule are doing excellent work and render a much-needed medical service, they cannot, for lack of facilities and staff, attempt to provide diagnosis and treatment for every medical or surgical condition. What they should or should not attempt depends on a number of factors and calls for judgment on the part of the physicians in the community. At times the decision is difficult and debatable.

In this issue Drs. Ross and Pick (page 49) present the record of the management and treatment of infantile pyloric stenosis in a community hospital. Their results are most satisfactory. However, their experience cannot be looked upon as giving carte blanche to every community hospital to undertake the treatment of infants with pyloric stenosis. Fitchburg is a good-sized city of over 40,000 population, with a "community hospital" of over 200 beds. Both physicians had excellent training and have been certified by their Specialty Boards. This is something quite different from the situation existing in many smaller communities with local hospitals. As the authors clearly bring out, the important thing to be considered is the welfare and interests of the patient, and that false local pride should never be a factor in the decision as to whether treatment should be attempted locally or referral made to a large medical center. The answer cannot be a fixed or stereotyped one. We are particularly impressed with their honesty and judgment in referring certain babies to the large medical center for treatment.

If adequate treatment can be given, there are a number of reasons why ordinarily it is best for the patient to be treated locally. On the other hand, there are many conditions that are better referred. The dividing line will differ in community hospitals, depending on the individual facilities and the training and experience of the staff.